A New Case of Malignant Mixed Epithelial and Stromal Tumor of the Kidney with Rhabdomyosarcomatous Transformation

To the Editors:

We report a new case of an epithelial and stromal tumor of the kidney (MESTK) with sarcomatous mesenchymal transformation, rhabdomyosarcoma. The patient was a 62-year-old female complaining of left abdominal pain. A renal mass was discovered and a left radical transperitoneal nephrectomy and left paraaortic lymphadenectomy was performed, in addition to complete excision of a thrombosed renal vein up to its cava connection. Grossly the tumor measured 5×4.5×4 cm and was located at the lower pole of the kidney, protruding on the renal surface (Figure 1A); it reached sinus fat and macroscopically grew into the renal vein. It was a relatively well-circumscribed, cystic and solid white-tan tumor with a big cyst with clear fluid inside and some smaller and minute peripheral cysts. The mass had a soft consistency, focal necrosis and hemorrhage. Histologically it was a biphasic tumor with benign epithelial cysts and a variably cellular surrounding mesenchyma (Figure 1B). Sometimes it was bland and focally sclerosed, or denser, fascicular and frequently sarcomatous. Cysts were lined by Müllerian (cuboidal, columnar, ciliated) and hobnailed epithelium. Some smaller cysts appeared forming aggregates, with light pink secretion inside; a few larger cysts had a phyllodes-like overgrowth of surrounding stroma (Figure 2A). Cysts appeared surrounded by “cuffs” of bland, dense, spindle cell stroma (sometimes ovarian-like) admixed with occasional desmin and myogenin-positive bizarre multinucleated cells, rhabdomyoblasts (Figures 3 and 4) which became more common and confluent towards the center of the mass, interspersed with bland, edematous, occasional hemangiopericytic-like areas with short-plump spindle cells, isolated calcifications and collagenous and hyalinized foci. Sarcomatous stroma was predominant (75% of the total). In most active areas there were a maximum of 12 mitotic figures/10 high-power field, some atypical. There were no carcinomatous elements or other heterologous, PEComatous, clear-cell aggregates or blastema components after sampling the entire tumor specimen. Lymphovascular sarcomatous invasion was frequent. The renal vein contained a neoplastic thrombus. Sinus fat tissue was focally infiltrated by the sarcomatous component. Nonneoplastic kidney had no relevant lesions. Hilar, periadrenal, paraaortic lymph nodes and left adrenal gland were free of tumor. Immunohistochemical studies showed that epithelia expressed cytokeratin (CK) AE1/3, CK7, EMA and CK5/6. Benign stromal cells were diffusely positive for Vimentin (Vim), CD10, smooth muscle actin (SMA), desmin and CD56. Stromal pericystic cells intensively expressed bcl-2...
Densely cellular atypical fascicular mesenchyma was Vimentin, SMA and desmin positive (while CD99, S100, HMB-45, EMA, myogenin and bcl-2 were negative). Pleomorphic, bizarre sarcomatous areas were SMA, myogenin and desmin positive (Figures 3 and 4); Ki-67 index was around 80% in most active areas. Isolated estrogen receptor reactivity was found only in bland MESTK stroma at the periphery of the tumor (negative for progesterone receptors). PCR-RNA results for SYT-SSX1, SYT-SSX2, PAX3-FKHR and PAX7-FKHR translocations were negative. She started with radiotherapy and one year afterwards she had surgery for a conventional colon adenocarcinoma (pT3N0). A multiplex PCR test to determine microsatellite instability status (MSI) with an MSI kit (Promega Biotech Ibérica S.L., Alcobendas, Madrid, Spain) for BAT-25, BAT-26, NR-21, NR-24 and MONO-27 in the renal and large bowel tumor gave negative results. Three years after the nephrectomy, she was alive with evidence of disease: increasing metastatic lung nodules and hilar mass, its origin not otherwise proven (either colonic or renal) in spite of a lung biopsy (unsatisfactory). The patient refused other diagnostic procedures due to dyspnea and a bad general condition.

MESTK is a recently described renal tumor with very few reported malignant cases. Malignant MESTKs basically have a sarcomatous overgrowth, usually undifferentiated sarcoma. The present case had a solid fascicular sarcomatous component with frequent bizarre, multinucleated and pleomorphic cells (rhabdomyoblasts), desmin and myogenin positive. There were variably sized (Figure 2B) and CD10. (Figure 2B) and CD10. Densely cellular atypical fascicular mesenchyma was Vimentin, SMA and desmin positive (while CD99, S100, HMB-45, EMA, myogenin and bcl-2 were negative). Pleomorphic, bizarre sarcomatous areas were SMA, myogenin and desmin positive (Figures 3 and 4); Ki-67 index was around 80% in most active areas. Isolated estrogen receptor reactivity was found only in bland MESTK stroma at the periphery of the tumor (negative for progesterone receptors). PCR-RNA results for SYT-SSX1, SYT-SSX2, PAX3-FKHR and PAX7-FKHR translocations were negative. She started with radiotherapy and one year afterwards she had surgery for a conventional colon adenocarcinoma (pT3N0). A multiplex PCR test to determine microsatellite instability status (MSI) with an MSI kit (Promega Biotech Ibérica S.L., Alcobendas, Madrid, Spain) for BAT-25, BAT-26, NR-21, NR-24 and MONO-27 in the renal and large bowel tumor gave negative results. Three years after the nephrectomy, she was alive with evidence of disease: increasing metastatic lung nodules and hilar mass, its origin not otherwise proven (either colonic or renal) in spite of a lung biopsy (unsatisfactory). The patient refused other diagnostic procedures due to dyspnea and a bad general condition.

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cysts with Müllerian-like and hobnailed epithelium and cuffs of densely bcl-2 positive ovarian-like stroma with some occasional atypical multinucleated desmin positive stromal cells; this could suggest a gradual transformation of the stroma into a denser heterologous pleomorphic sarcoma towards the center of the mass. Actually the diagnosis becomes straightforward due to its characteristic morphology and immunophenotype, with areas of benign MESTK. Several differential diagnoses arise: the predominant solid pattern and morphology argue against adult cystic nephroma, though both belong to the same wide spectrum of disease.\textsuperscript{1-3,5,8,10} Primary synovial sarcoma is another entity to consider, but the morphology, immunophenotype and the lack of its specific translocation do not support that diagnosis. A sarcomatoid clear renal cell carcinoma, other primary pure malignant renal mesenchymal neoplasias, cystic renal tumors like angiomyolipomas with epithelial cysts and metastases were easily disregarded. The few reported malignant MESTKs had a sarcomatous proliferation,\textsuperscript{5,6,8-10} usually undifferentiated sarcoma. Those series included 7 cases, with ages ranging from 24–56 years and tumor sizes from 6–26 cm, with sarcomatous component mainly unclassified (4 cases), synovial sarcoma-like sarcoma (2 cases), and heterologous (rhabdomyosarcoma and chondrosarcoma) (1 case). In the present case desmin positive tumor sarcoma cells were occasionally arranged in an alveolar pattern. Synovial sarcoma and alveolar rhabdomyosarcoma were excluded after negative PCR-RNA results for SYT-SSX1, SYT-SSX2, PAX3-FKHR and PAX7-FKHR translocations. Mixed epithelial and stromal renal tumor (MESTK) belongs to the spectrum of cystic nephroma (CN)-MESTK. It is a neoplasm with strong hormonal influence that typically occurs in peri-menopausal women. A recent study\textsuperscript{1} found non-random inactivation of X-chromosome in MESTK epithelia and stroma, supporting a common cell of origin. In summary, we describe a new case of malignant MESTK with benign areas merging with a predominant rhabdomyosarcoma component, with negative PCR-RNA results for SYT-SSX1, SYT-SSX2, PAX3-FKHR and PAX7-FKHR translocations and also for an MSI status.

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References


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Smooth Muscle Metaplasia in Renal Cell Carcinoma: A Specific Histological Entity or an Aspecific Stromal Reaction?

To the Editors:

Classification schemes of renal epithelial neoplasms have evolved greatly over the past two decades. Detailed morphological studies incorporating contemporary immunohistochemical and molecular techniques have resulted in the current classification of renal epithelial neoplasms as outlined in the 2004 World Health Organization monograph. Clear cell, papillary and chromophobe carcinomas account for 85–90% of carcinomas seen in routine practice. The remaining 10–15% of carcinomas consist of rare sporadic and hereditary tumors, some of which have been long recognized, but many of which have emerged only recently as distinct entities. In addition there is a group of rare, recently described carcinomas which includes oncocytic papillary renal cell carcinoma, follicular renal carcinoma clear cell, papillary carcinoma and leiomyomatous renal cell carcinoma. Related to the last two entities, it has been accepted that the stroma of clear cell papillary renal cell carcinoma (RCC) not infrequently demonstrates smooth muscle metaplasia. The extreme end of this spectrum are likely tumors reported as renal angiomyoadenomatous tumor (RAT) to reflect the prominence of smooth muscle. RAT tumors appear to have the same clinicopathologic and immunohistochemical characteristics as clear cell papillary RCC. Despite vigorous arguments to the contrary, a recent abstract comparing these two entities suggests that they can now be considered as a spectrum in the same category of tumors. It should be remembered, however, that smooth muscle stromal metaplasia and proliferation are not entirely specific to this entity. For example, smooth muscle stromal metaplasia has been reported in association with clear cell RCC. In 2006, five cases of renal cell carcinoma described as having angioleiomyoma-like stroma were described. Four similar cases had been previously reported in which angioleiomyoma-like stroma was admixed with clear cells that were interpreted as being either renal cell carcinoma or benign. Since the publication of the original series, new reports have detailed the features of further cases, describing a spectrum of clear cell renal cell carcinoma with a variable amount of leiomyomatous stroma. In the described cases tumors are composed of nests, cords and sheets of epithelial cells frequently forming solid areas, tubules or papillary structures. There is minimal nuclear pleomorphism with abundant clear cytoplasm. The muscular component consisted of poorly cellular, leiomyomatous bundles, which greatly differed from that of angiomyolipoma. This com-
ponent is often pronounced at the periphery and in some cases appears to extend into adjacent renal tissue or into perirenal adipose tissue. The epithelial component of the tumor showed positive immunoreexpression of cytokeratins AE1/AE3, CK7 and CAM 5.2, CD-10, S-100 protein (focal), EMA and vimentin. The stroma component was positive for smooth muscle actin, caldesmon, desmin and vimentin and negative for HMB45, CD117, cytokeratins, EMA, ER and PR. The muscle bundles encircled the whole tumor and intimately intermingled with the epithelial component. The stroma has the appearance of mature smooth muscle sometimes with scattered, often dilated vascular spaces. These leiomyomatous bands formed focally abortive vessels, which had incomplete and irregular walls and lacked an elastic layer. Although most of the reported tumors showed prominent angioleiomyoma-like stroma, genetic studies on these tumors are contradictory. In some cases fluorescence in situ hybridization showed loss of von Hippel Lindau and fragile histidine triad, with loss of chromosome 3 typical of clear cell RCC. It should be noted, however, that recent data has questioned the relationship of these smooth muscle rich neoplasms to clear cell RCC. It should be noted, how-ever, that recent data has questioned the relation-

References


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Authors’ Comment: The following interesting report was published shortly before publication of our letter: Limani R, Luci LG, Marušić Z, Gatalica Z,

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