

Case Report

Malignant mixed epithelial and stromal tumor of the kidney: the second male case and review of literature

Liang Zou, Xiuming Zhang, Hua Xiang

Department of Pathology, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, Zhejiang Province, China

Received December 11, 2013; Accepted April 10, 2014; Epub April 15, 2014; Published May 1, 2014

Abstract: Mixed epithelial and stromal tumor of the kidney is a recently described neoplasm that predominantly affects perimenopausal women. Although typically benign, few cases with malignant features have been reported. Here, we report the second male case of malignant mixed epithelial and stromal tumor of the kidney with sarcomatous transformation. The patient presented with abdominal discomfort and right flank pain. Computed tomography (CT) of the abdomen revealed a large mass arisen from the right kidney with solid and focal cystic components. The patient underwent right radical nephrectomy. Histologic sections showed benign and malignant components. The benign component consisted of multiple tubules and variably sized cysts lined by benign epithelium. The malignant component was predominantly composed of undifferentiated cellular spindle cell sarcoma. By immunohistochemical studies, the epithelial component was positive for cytokeratins and epithelial membrane antigen (EMA). The stromal component displayed strong immunohistochemical expression of vimentin, CD-99, bcl-2; and was negative for cytokeratins, desmin, SMA, S-100, estrogen receptor (ER) and progesterone receptor (PR). Analysis by reverse transcriptase polymerase chain reaction (RT-PCR) failed to identify the SYT-SSX1 or SYT-SSX2 fusion transcripts characteristic of synovial sarcoma. Subsequently adjuvant chemotherapy was given. The patient developed a local recurrent tumor 9 months after operation.

Keywords: Mixed epithelial and stromal tumor, sarcomatous transformation, malignant

Introduction

Mixed epithelial and stromal tumor of the kidney (MESTK) is a distinct category of renal entity unifying several neoplasms such as adult type of mesoblastic nephroma, cystic hamartoma of the renal pelvis and adult type of cystic nephroma [1-4]. The lesions occur nearly always in women, especially in perimenopausal women [3, 4]. The tumor is typically solid and cystic. Microscopically, the tumor is composed of biphasic components including variable-sized cysts and tubules embedded in the spindle cell stroma [4-6]. The epithelial elements may display a tubules, microcysts or macrocysts with abundant eosinophilic cytoplasm and a hobnail appearance. The spindle-cell stromal component ranges in appearance from scar like fibrous tissue to leiomyoma like interlacing fascicles, usually with a mixture of both. Sometimes ovarian-like stroma or solitary fibrous tumor is also present [1, 6, 7].

Although MESTK is characterized by a benign histology and clinical course; extremely rare cases of MESTK with malignant transformation have been reported [2, 8-13, 22]. To our knowledge, the overwhelming majority of previously reported MESTK with malignant transformation occurred in women, only one case occurred in an old man [22]. Herein, we report the second male case of MESTK with malignant transformation.

Clinical history

A 19-year-old man presented with abdominal discomfort and right flank pain for one month. He had no significant medical history or family history of any malignancy and no history of treated with hormone. Physical examination revealed a 30-cm, immobile, non-tender mass involving the right abdomen. He demonstrated no clinical abnormalities associated with his kidney lesion and macroscopic hematuria. All of

Malignant mixed epithelial and stromal tumor of the kidney

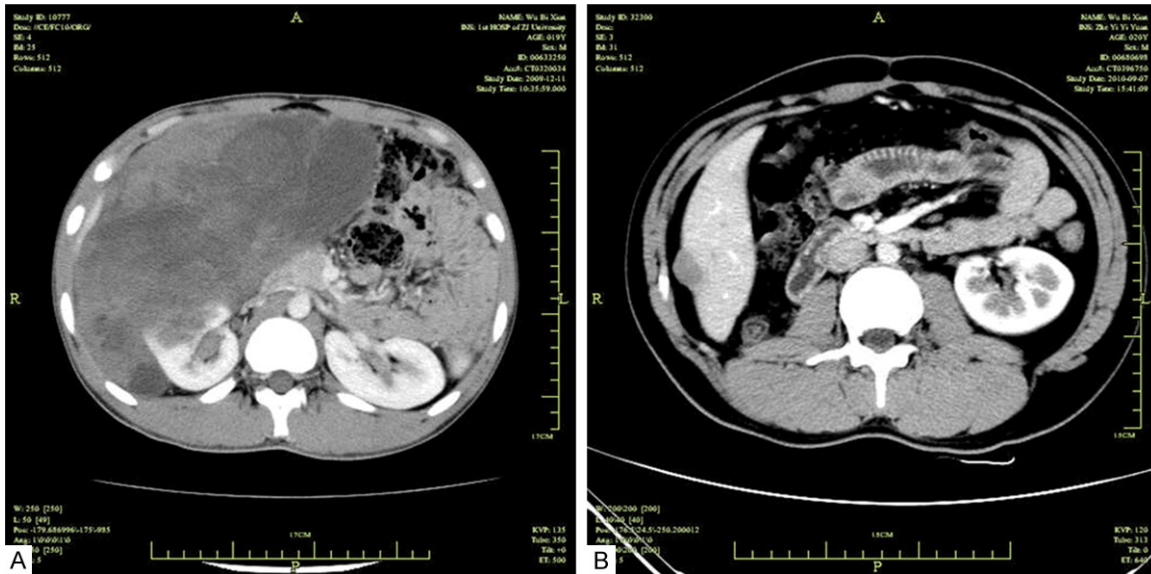


Figure 1. A: Computed tomography (CT) of the abdomen revealed a large mass arisen from the right kidney. B: CT scanning showed a local recurrent tumor that has invaded the right liver.

his laboratory data were within the normal ranges. Computed tomography of the abdomen revealed a large mass measuring 28×19×15 cm arisen from the right kidney (**Figure 1A**). The patient underwent right radical nephrectomy. Two cycles of adjuvant chemotherapy was subsequently given. Nine months after operation, he developed a local recurrent tumor that had invaded the right lateral body wall and right liver (**Figure 1B**).

Pathologic findings

Grossly, the right radical nephrectomy specimen contained a gray-brown, partially necrosis 28.0×19.0×15.0-cm mass located in the upper pole of the kidney. The tumor involved the renal parenchyma and infiltrated into the renal pelvis and perinephric adipose tissue. The tumor was composed of predominantly solid and cystic components; the former was gray-brown and firm and the latter contained grossly obvious cysts and tubules, with the largest cyst measuring 1.5 cm in diameter. Microscopically, pathological examination showed an unusual biphasic tumor consisting of solid and cystic components (**Figure 2A**). In the cystic areas, the cysts or tubules varied greatly in size from 0.1 to 1.5 cm and were lined by a single layer of cuboidal cells with eosinophilic cytoplasm and hobnail appearance. The lining epithelial cells were relatively uniform and showed no signifi-

cant cytologic atypia or mitosis (**Figure 2B**). Most of the epithelial cells were bland and seemed benign. Septa around cystic spaces were formed by spindle-cell stroma with uneven cellularity focally displaying ovarian-like features. Most of the spindle cells displayed striking pleomorphism, prominent nucleoli, a high mitotic rate (about 30 to 40 mitoses per 10 high-power fields) (**Figure 2C**). The stromal components formed interlacing bundles and small fascicles with focal necrosis and infiltrated the renal parenchyma. In some areas, the stroma around the cysts or tubules seemed benign consisting of bland spindle cells with no evidence of atypical and high mitotic activity cells. The benign MESTK was considered as a diagnosis for this area. Overall, the benign MESTK component comprised approximately 15% of the entire tumor.

In immunohistochemical studies, the epithelial component were positive for wide spectrum cytokeratin and EMA; the stromal component showed strong diffuse positivity for vimentin, CD99 (**Figure 3A**), bcl-2 (**Figure 3B**) and focally positivity for WT-1 and EMA. Both epithelial and stromal components were negative for CD10, CD34, CD117, S-100, desmin, SMA, HMB45, Melan-A, Syn, CGA, ER and PR.

RT-PCR assay to detect the chimeric fusion transcripts SYT-SSX1 and SYT-SSX2 performed on RNA extracted from formalin-fix-ed, paraffin-embedded tissue was negative.

Malignant mixed epithelial and stromal tumor of the kidney

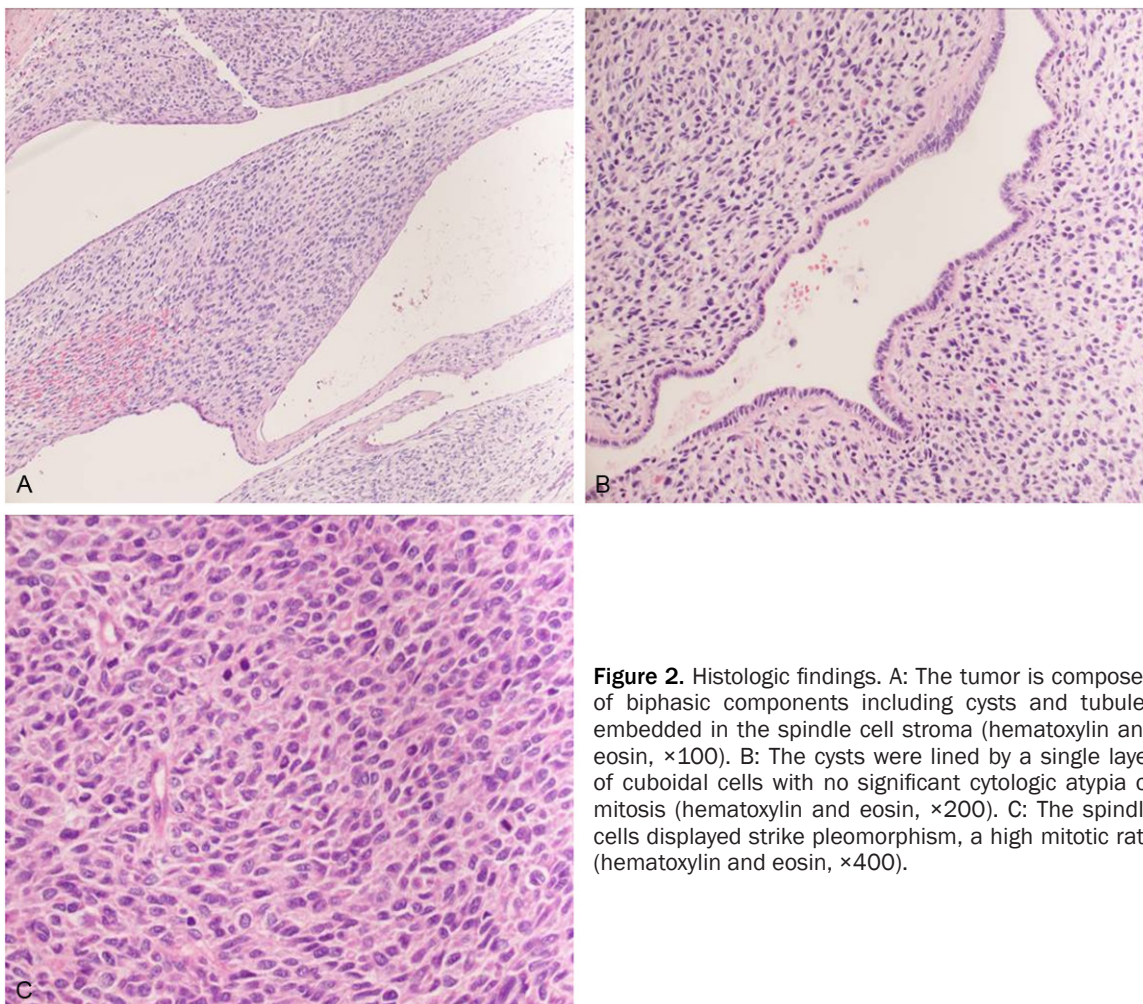


Figure 2. Histologic findings. A: The tumor is composed of biphasic components including cysts and tubules embedded in the spindle cell stroma (hematoxylin and eosin, $\times 100$). B: The cysts were lined by a single layer of cuboidal cells with no significant cytologic atypia or mitosis (hematoxylin and eosin, $\times 200$). C: The spindle cells displayed strike pleomorphism, a high mitotic rate (hematoxylin and eosin, $\times 400$).

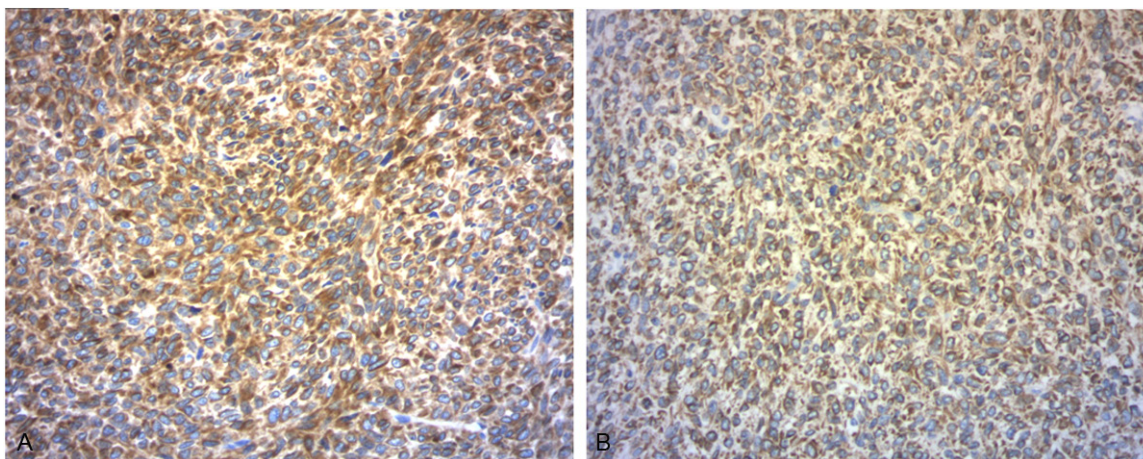


Figure 3. Immunophenotypic findings. The malignant stroma showed strong positivity for CD99 (A, immunohistochemistry $\times 100$) and bcl-2 (B, immunohistochemistry $\times 100$).

Both histological and immunohistochemical features of recurrent tumor were similar with pri-

mary tumor, but stromal components of the former showed more significant cytologic atypia

Malignant mixed epithelial and stromal tumor of the kidney

and higher mitotic rate (up to 8 mitoses per 1 high-power field) compared with the latter.

Discussion

In our case, the tumor is composed of biphasic components including variable-sized cysts and tubules embedded in the spindle cell stroma. Most of the spindle cells displayed striking pleomorphism, prominent nucleoli and a high mitotic rate. Based on the clinical and morphological findings, we consider this case as a malignant mixed epithelial and stromal tumor of the kidney.

The term “mixed epithelial and stromal tumor of the kidney” is first defined by Michal and Syrucek in 1998 [1]. It is a rare benign neoplasm of unknown histogenesis that almost exclusively occurs in perimenopausal women (male to female ratio, 1:10) [14]. Many of the affected women reported a history of long-term oral estrogen therapy that suggested a possible hormonal pathogenetic mechanism involved in MESTK [4, 15]. But not all MESTK cases implicated a hormonal mechanism [16, 17]. Most patients presented with symptoms such as hematuria, flank pain, a palpable mass, or urinary tract infection. Approximately 25% of MESTKs were incidentally identified [4, 15].

Malignant transformation, recurrence, and metastasis are rare in MESTK. However, to date ten cases of malignant MESTK have been reported in the literature [2, 8-13, 22]. Nine cases occurred in women (mean, 49.3 years; range, 24-84 years), only one case occurred in an old man [22]. The features of malignancy can be observed in either epithelial or mesenchymal components. The malignant transformation of mesenchymal components includes synovial sarcoma [2], rhabdomyosarcoma [11-13], chondrosarcoma [11, 13] and unclassified sarcoma [8, 9, 22]. Recently, two cases of malignant MESTK with carcinomatous component have been reported [11, 13].

ER and PR expression have been described in the mesenchymal element in most cases of MESTK containing ovarian-type stroma. A recent report revealed 62% of ER and 85% of PR expression in stromal component of benign MESTK [18]. Although focal ER and PR expression has been described in malignant MESTK, ER and PR expression are not by themselves diagnostic of MESTK, and characteristic mor-

phologic features should take precedence [11, 14]. To make a diagnosis of malignant transformation of MESTK, Jung SJ proposed that following criteria should be fulfilled [11]: (1) tumor location—the epicenter of the tumor should be in the kidney; (2) clear-cut evidence of benign epithelial and stromal components with tubules or cysts lined by bland epithelial cells and spindle cell stroma resembling that of ovarian-type stroma; (3) morphologically malignant components should be intimately associated with benign counterparts; and finally, (4) primary renal sarcoma or metastasis should be ruled out.

The major differential diagnosis includes leiomyosarcoma, synovial sarcoma and sarcomatoid renal cell carcinoma. Although leiomyosarcoma is the most common mesenchymal tumor arising in the kidney, it contains neither neoplastic epithelial component nor entrapped tubules, because its growth is expansive rather than infiltrative. Monophasic and biphasic synovial sarcomas can rarely occur as a primary renal tumor. Several features of malignant MEST are also defining morphologic features observed in primary renal synovial sarcomas, especially gross or microscopic cysts and tubules lined by hobnail epithelium, immunoreactivity for cytokeratin in the epithelial component, and variably dense spindle-cell stroma with occasional short fascicles and a moderate degree of mitotic activity in biphasic synovial sarcoma [2, 19-21]. However, the prominent subepithelial condensation of the stroma (ovarian-like stroma) is a distinctive feature of MESTK and is not observed in renal synovial sarcoma. Furthermore, their epithelial cells are usually cuboidal or polygonal and tend to form solid nests, glandular or tubular structures with obvious cytologic atypia [11, 20, 21], whereas the epithelial cells in the present cases lacked atypia and were reminiscent of normal renal tubules. In monophasic synovial sarcomas, there is no cystic structure, but dilation of entrapped renal tubule can cause confusion with MESTK. In the present cases, the epithelial cells were negative for CD10, whereas peripheral proximal convoluted tubules were positive for this marker. In addition, both histological and immunohistochemical features of recurrent tumor in right lateral body wall were similar with primary tumor. All of these findings demonstrated that epithelial cells were neoplastic epithelial components not entrapped

Malignant mixed epithelial and stromal tumor of the kidney

tubules. Otherwise, no chimeric transcripts for synovial sarcoma were identified in our case. A sarcomatoid component occurs in approximately 5% of all renal cell carcinoma. Cystic areas with benign epithelial cell lining, tubules, and benign spindle cell stroma are not seen in sarcomatoid renal cell carcinoma. In addition, the sarcomatoid renal cell carcinoma should be immunohistochemically positive for epithelial markers [11].

In summary, MESTK represents a benign tumour of the kidney, which is predominately observed in perimenopausal women. Only rare cases of malignant transformation have been published. We present a case of MESTK with undifferentiated sarcoma transformation. To the best of our knowledge, this is the second male case of malignant MESTK in the literature. The histogenesis, pathogenetic mechanism and clinical behavior of this unique malignant neoplasm require further studies on more cases.

Disclosure of conflict of interest

The authors have disclosed that they have no significant relationships with any commercial companies pertaining to this article.

Address correspondence to: Dr. Hua Xiang, Department of Pathology, The First Affiliated Hospital, College of Medicine, Zhejiang University, No.79 Qingchun Road, Hangzhou, Zhejiang 310003, China. Tel: +86-571-87236362; Fax: +86-571-87236364; E-mail: zhangxiuming83@163.com

References

- [1] Michal M, Syrucek M. Benign mixed epithelial and stromal tumor of the kidney. *Pathol Res Pract* 1998; 194: 445-448.
- [2] Svec A, Hes O, Michal M, Zachoval R. Malignant mixed epithelial and stromal tumor of the kidney. *Virchows Arch* 2001; 439: 700-702.
- [3] Michal M. Benign mixed epithelial and stromal tumor of the kidney. *Pathol Res Pract* 2000; 196: 275-276.
- [4] Adsay NV, Eble JN, Srigley JR, Jones EC, Grignon DJ. Mixed epithelial and stromal tumor of the kidney. *Am J Surg Pathol* 2000; 24: 958-970.
- [5] Bisceglia M, Galliani CA, Senger C, Stallone C, Sessa A. Renal cystic diseases: a review. *Adv Anat Pathol* 2006; 13: 26-56.
- [6] Michal M, Hes O, Bisceglia M, Simpson RH, Spagnolo DV, Parma A, Boudova L, Hora M, Zachoval R, Suster S. Mixed epithelial and stromal tumors of the kidney. A report of 22 cases. *Virchows Arch* 2004; 445: 359-367.
- [7] Jevremovic D, Lager DJ, Lewin M. Cystic nephroma (multilocular cyst) and mixed epithelial and stromal tumor of the kidney: a spectrum of the same entity? *Ann Diagn Pathol* 2006; 10: 77-82.
- [8] Nakagawa T, Kanai Y, Fujimoto H, Kitamura H, Furukawa H, Maeda S, Oyama T, Takesaki T, Hasegawa T. Malignant mixed epithelial and stromal tumors of the kidney: a report of the first two cases with a fatal clinical outcome. *Histopathology* 2004; 44: 302-304.
- [9] Yap YS, Coleman M, Olver I. Aggressive mixed epithelial-stromal tumor of the kidney treated with chemotherapy and radiotherapy. *Lancet Oncol* 2004; 5: 747-749.
- [10] Bisceglia M, Bacchi CE. Mixed epithelial-stromal tumor of the kidney in adults: two cases from the Arkadi M. Rywlin slide seminars. *Adv Anat Pathol* 2003; 10: 223-233.
- [11] Jung SJ, Shen SS, Tran T, Jun SY, Truong L, Ayala AG, Ro JY. Mixed epithelial and stromal tumor of kidney with malignant transformation: report of two cases and review of literature. *Hum Pathol* 2008; 39: 463-468.
- [12] Sukov WR, Chevillie JC, Lager DJ, Lewin JR, Sebo TJ, Lewin M. Malignant mixed epithelial and stromal tumor of the kidney with rhabdoid features: report of a case including immunohistochemical, molecular genetic studies and comparison to morphologically similar renal tumors. *Hum Pathol* 2007; 38: 1432-1437.
- [13] Kuroda N, Sakaida N, Kinoshita H, Matsuda T, Hes O, Michal M, Okamoto S, Nagashima Y, Tanaka Y. Carcinosarcoma arising in mixed epithelial and stromal tumor of the kidney. *AP-MIS* 2008; 116: 1013-1015.
- [14] Mohanty SK, Parwani AV. Mixed Epithelial and Stromal Tumors of the Kidney: An Overview. *Arch Pathol Lab Med* 2009; 133: 1483-1486.
- [15] Lane BR, Campbell SC, Remer EM, Fergany AF, Williams SB, Novick AC, Weight CJ, Magi-Galluzzi C, Zhou M. Adult cystic nephroma and mixed epithelial and stromal tumor of the kidney: clinical, radiographic, and pathologic characteristics. *Urology* 2008; 71: 1142-1148.
- [16] Kwon JE, Kang JH, Kwon GY. Mixed epithelial and stromal tumor of the kidney: a case report. *J Korean Med Sci* 2007; 22: 159-162.
- [17] Sountoulides P, Koptsis M, Metaxa L, Theodosiou A, Kikidakis D, Filintatzi C, Paschalidis K. Mixed epithelial and stromal tumor of the kidney (MEST) simulating an upper tract TCC. *Can Urol Assoc J* 2012; 6: 23-26.
- [18] Turbiner J, Amin MB, Humphrey PA, Srigley JR, De Leval L, Radhakrishnan A, Oliva E. Cystic nephroma and mixed epithelial and stromal tumor of kidney: a detailed clinicopathologic

Malignant mixed epithelial and stromal tumor of the kidney

- analysis of 34 cases and proposal for renal epithelial and stromal tumor (REST) as a unifying term. *Am J Surg Pathol* 2007; 31: 489-500.
- [19] Shannon BA, Murch A, Cohen RJ. Primary renal synovial sarcoma confirmed by cytogenetic analysis: a lesion distinct from sarcomatoid renal cell carcinoma. *Arch Pathol Lab Med* 2005; 29: 238-240.
- [20] Kim DH, Sohn JH, Lee MC, Yoon GS, Hashimoto H, Sonobe H, Ro JY. Primary synovial sarcoma of the kidney. *Am J Surg Pathol* 2000; 24: 1097-1104.
- [21] Argani P, Faria PA, Epstein JI, Reuter VE, Perlman EJ, Beckwith JB, Ladanyi M. Primary renal synovial sarcoma: molecular and morphologic delineation of an entity previously included among embryonal sarcomas of the kidney. *Am J Surg Pathol* 2000; 24: 1087-1096.
- [22] Suzuki T, Hiragata S, Hosaka K, Oyama T, Kuroda N, Hes O, Michal M. Malignant mixed epithelial and stromal tumor of the kidney: Report of the first male case. *Int J Urol* 2012; 20: 448-450.