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Mixed epithelial and stromal tumor of kidney with renal vein extension: an unusual case report and review of literature

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Summary. Mixed epithelial and stromal tumor of kidney (MESTK) is a rare but distinct renal complex neoplasm composed of a mixture of mesenchymal and epithelial elements with characteristic ovarian-type stroma. Due to its relative rarity, little is known about the histogenesis and prognostic factors of this tumor. Although most reported cases display bland histological features and benign clinical course, a few cases of malignant MESTK have been described. We report an unusual case of MESTK in a 50-year-old female patient with renal venous involvement. Macroscopically, the tumor was solid and unencapsulated in the central region of left kidney. There was a polypoid mass with slender pedicle found to extend into the renal vein forming an intravenous tumor thrombus. Histologically, both renal and intravenous mass were composed of bland spindle-shaped cells and round dilated tubules lined by epithelium without any cytological atypia. The spindle cells were diffusely positive for smooth muscle actin and desmin, while tubules were positive for pan-cytokeratin (AE1/AE3). A diagnosis of MESTK with renal vein extension was made. The patient received no adjuvant treatment after radical nephrectomy. There was no sign of recurrence or metastasis of tumor found in a period of 16-month regular follow-up. To our knowledge, this is the first case of MESTK with renal vein extension, but lacking malignant histological appearance. Additional studies of MESTK with vein involvement will be needed to determine whether this imparts any adverse behavior, similar to other benign renal tumors with vascular involvement.

Key words: Renal tumor, Mixed epithelial and stromal tumor, Renal vein extension, Differential diagnosis

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Introduction

Mixed epithelial and stromal tumor of kidney (MESTK) is a rare renal tumor and only isolated case reports and small series are available in the literature. According to the World Health Organization (WHO) classification, this tumor is a complex neoplasm composed of a mixture of stromal and epithelial elements (Michal et al., 2016). Although this lesion has been initially regarded as benign tumor (Michal and Syrucek, 1998; Richter et al., 2010), a few cases of malignant MESTK with recurrence and metastasis have been reported in the literature. To the best of our knowledge, so far only 12 cases with malignant transformation in either epithelial or mesenchymal components have been described. Herein, we report a unique case of this clinical entity in a middle-aged female patient. In contrast to previous malignant cases, our case presents an unexpected finding of renal venous involvement, however, there are no malignant histological features displayed in either epithelial or mesenchymal components of the tumor. This might be the first presentation of MESTK with renal vein extension. The literature on this rare tumor is reviewed and its clinicopathological characteristics are discussed.

Material and methods

Clinical manifestation and management

A 50-year old female patient had suffered from intermittent left flank pain for 1 year before she developed gross hematuria. As a result, she was referred to our hospital for examination and treatment. She had no remarkable medical or family history, and no history of any trauma on back and abdomen. Physical examination showed the patient had a mild left flank knocking pain, but there was no fever, weight loss and no palpable lymphadenopathy or organomegaly. The laboratory results, including blood count, differential and liver function, were within the normal range. Routine urine analysis revealed microscopic hematuria (red blood cells, 3-4/HPF), but urine cytology was negative for malignancy. Abdominal computed tomography (CT) study revealed a well-circumscribed mass of 3.5×3.0×1.0 cm located in the central region of the left kidney, and protruding into the renal pelvic cavity. There was no evidence of lymph node or distant metastases, but left renal vein was observed to have a partial filling defect and was suggestive of renal venous tumor embolus (Fig. 1). In order to make a preoperative diagnosis, a CT guided needle biopsy was performed on left renal mass initially. A small piece of tumor tissue was obtained for histological examination. Microscopically, the lesion was entirely composed of spindle cells with plump nuclei and abundant cytoplasm. Mitotic figure and atypical nuclei were not present. Immunohistochemically, spindle cells were diffusely positive for smooth muscle actin (SMA) and desmin, but negative for pan-cytokeratin (AE1/AE3), epithelial membrane antigen (EMA), CD34, S-100, HMB-45 and Melan A. The Ki-67 (MIB-1) index was approximately 2%. Based on these findings, the diagnosis of benign renal leiomyoma was made. The intravenous lesion was suspected to be an intravenous leiomyoma.

A week after biopsy examination, left radical nephrectomy was undertaken. At surgery, the tumor was observed to arise from the submucosa of renal pelvic cavity, and grow as expansile mass protruding into the renal pelvic cavity. There was a clear demarcation between the tumor and the renal parenchyma. An intravenous mass located in left renal vein was also found. There was a narrow slender pedicle connecting intravenous polypoid mass to the renal tumor. The intravenous mass was bluntly separated from the wall of renal vein.

Histological process

The surgical specimens were routinely fixed in 10% neutral buffered formalin after surgery. The tissues were embedded in paraffin. Four micrometer-thick sections were stained with H&E and analyzed by immunohistochemistry or FISH assay. Immunohistochemical analyses were performed using the ChemMate Envision/HRP Kit and antibodies were obtained from Dako Cytomation (Carpinteria, CA, USA) and Santa Cruz Biotechnology (Santa Cruz, CA, USA). Slides were dewaxed and rehydrated routinely and then were treated with 10 millimole citrate buffer (pH 6.0) in a microwave for antigen retrieval. After incubation with diluted primary antibodies, slides were treated with the ChemMate Envision/HRP Kit for 30 min at room temperature followed by development with diamino-benzidine

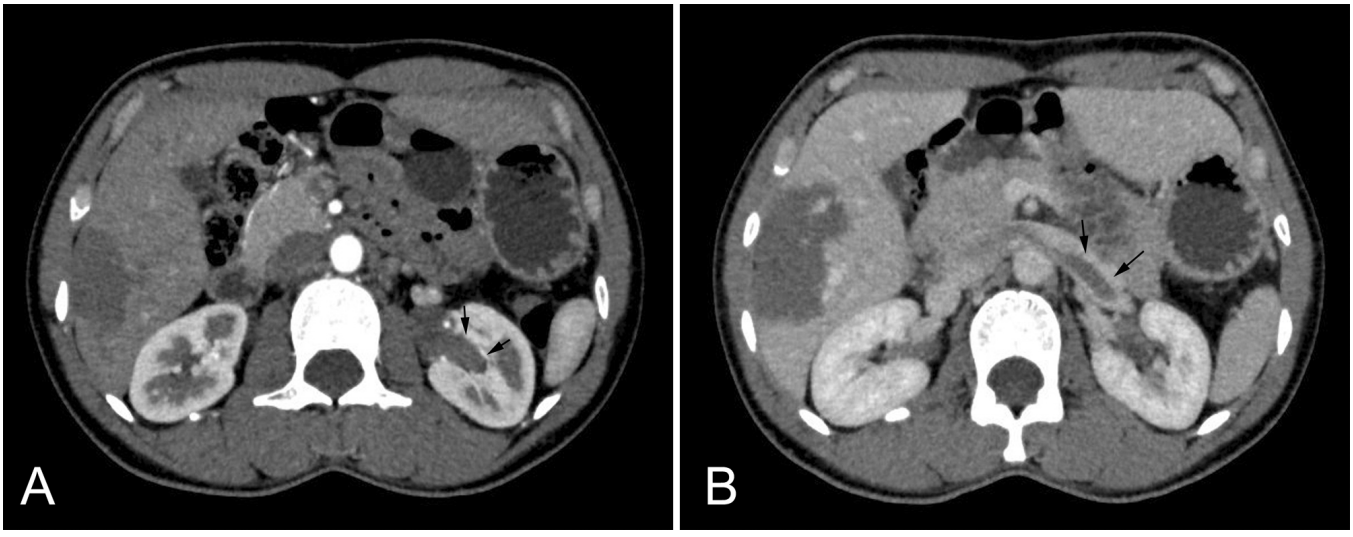

Fig. 1. Radiographic examination of the lesions. **A.** Computed tomography (CT) scan showed a well-circumscribed lesion located in the central region of left kidney, protruding into the renal pelvic cavity (black arrow). **B.** Contrast CT scan revealed a filling defect in the left renal vein and was suggestive of venous tumor embolu (black arrow).

(DAB) for visualization. The *ETV6* and *SYT* gene rearrangements were detected by FISH assay using Vysis Break Apart FISH Probe, respectively (Abbott Molecular, Abbott Park, IL, USA).

Results

Pathological findings

Macroscopically, the renal mass measured 3.5×3.0×1.0 cm and was observed in the central region of the kidney. The mass was solid, unencapsulated and well circumscribed. Cut surface of tumor was firm and grayish in color. An intravenous polypoid mass with slender pedicle, measuring 5.2 cm in length, was observed to link the main body of renal mass. There was neither cyst nor necrosis found in both masses (Fig. 2). Microscopically, the histological appearance of tumor, resembling that of biopsy examination, exhibited fascicles of bland ovarian-stroma like spindle cells with eosinophilic cytoplasm lacking mitotic figures. Hypocellular areas with densely collagenous stroma were also seen. Unlike the biopsy, however, epithelial component, forming round and regular tubules with microcystic dilatation could be observed the interspersed throughout the spindle cell component. The tubules were lined by bland cuboidal or flattened epithelium. Mitotic figures, hemorrhage, and necrosis were not observed (Fig. 3). The histological morphology of intravenous mass was similar to that of renal mass.

Immunohistochemical and FISH assay

Immunohistochemically, the epithelial component was positive for pan-cytokeratin (AE1/AE3), cytokeratin 7 and EMA. Spindle cells component showed strong positivity for vimentin, SMA and desmin, and focal positive for estrogen receptor (ER). Ki-67 index was less than 2%. However, both epithelial and spindle cell components were negative for CD10, S-100, CD34, HMB45, Melan A and progesterone receptors (PR). There was neither *ETV6* nor *SYT* gene fusion detected in the tumor, which excluded the diagnosis of cellular mesoblastic nephroma or synovial sarcoma of kidney (Fig. 4).

Based on the pathological findings, the renal mass was finally diagnosed as MESTK according to WHO diagnostic criteria, with the unexpected finding of renal venous involvement.

Postoperative recovery was uneventful without surgical complications. Considering that hematogenous involvement could occur, the patient was referred to a whole body positron emission tomography (PET)/CT study to search for the potentially secondary tumor, but no abnormality was found. After final histological diagnosis, the patient was discharged from the hospital without any adjuvant treatment. A regular follow-up for 16 months was performed, and there was no sign of

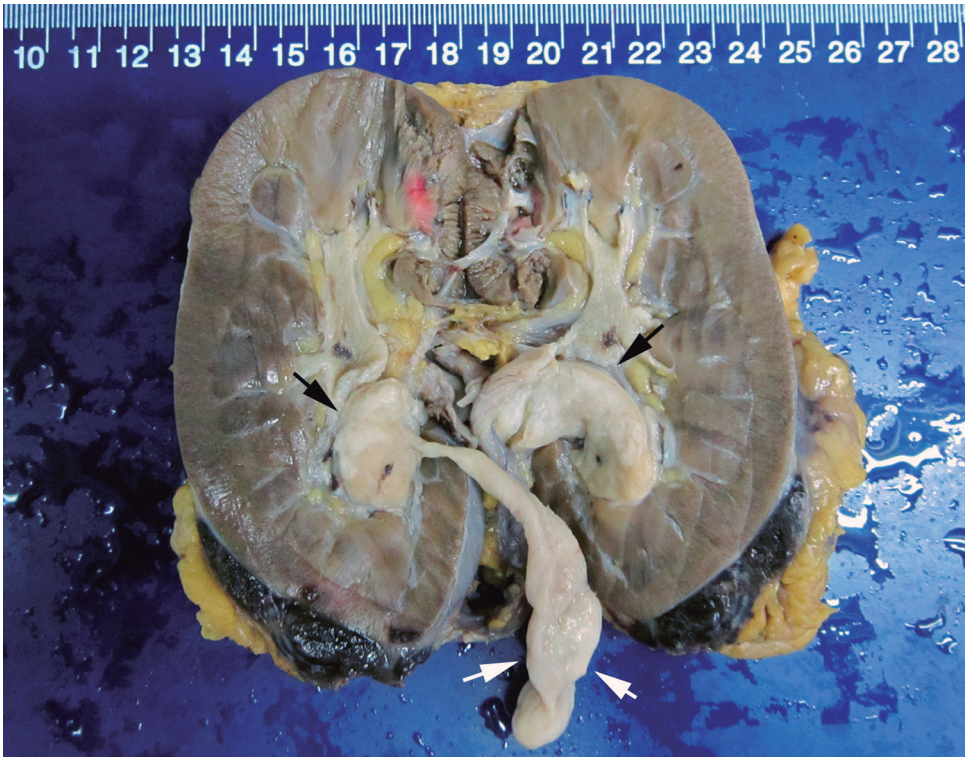

Fig. 2. Gross examinations of resected renal and intravenous masses. The masses were grayish, nodular lesions without a fibrous capsule. The mass was observed to extend to the renal pelvic cavity (black arrow), and a slender pedicle was connected to the intravenous polypoid mass (white arrow). There were no cystic or necrotic areas found in masses.

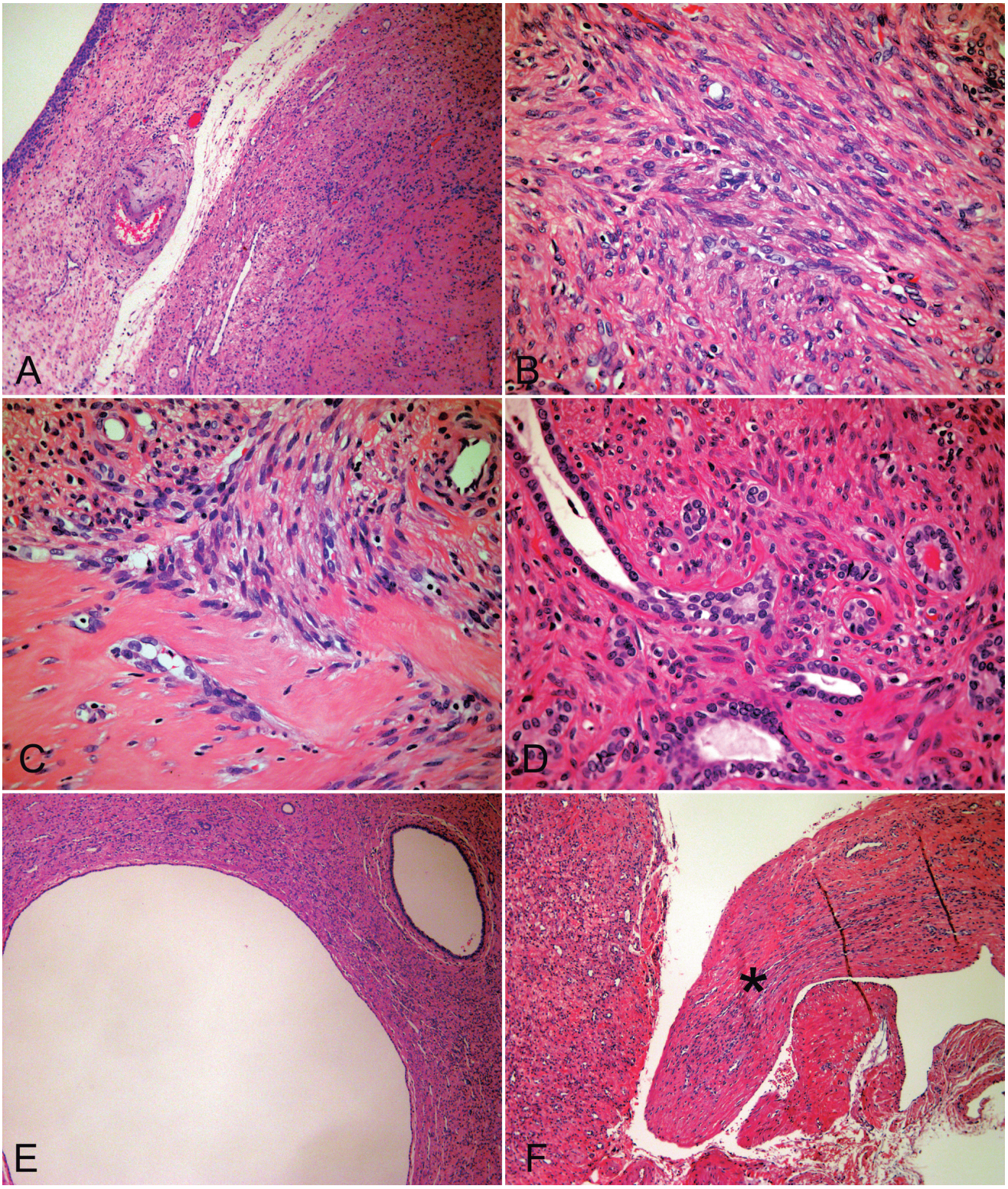

Fig. 3. Photomicrographs of the renal masses. **A.** At lower power field, the renal mass was observed to arise from the submucosa of renal pelvic cavity. **B.** The tumor was composed of fascicles of bland spindle cells with plump nuclei and abundant cytoplasm, without mitotic figure and cellular atypia. **C.** Hypocellular areas with densely collagenous stroma were also seen in the spindle cell component. **D.** Epithelial component, forming round and regular tubules could be observed interspersed throughout the spindle cell component. The tubules were lined by bland cuboidal or flattened epithelium. Mitotic figures, hemorrhage, and necrosis were not observed. **E.** Epithelial tubules with microcystic dilatation could be observed. **F.** The narrow slender pedicle (*) composed of spindle cells resembling the histological appearance of renal mass was observed connected to the intravenous polypoid mass. H&E staining. A, x 100; B-F, x 400.

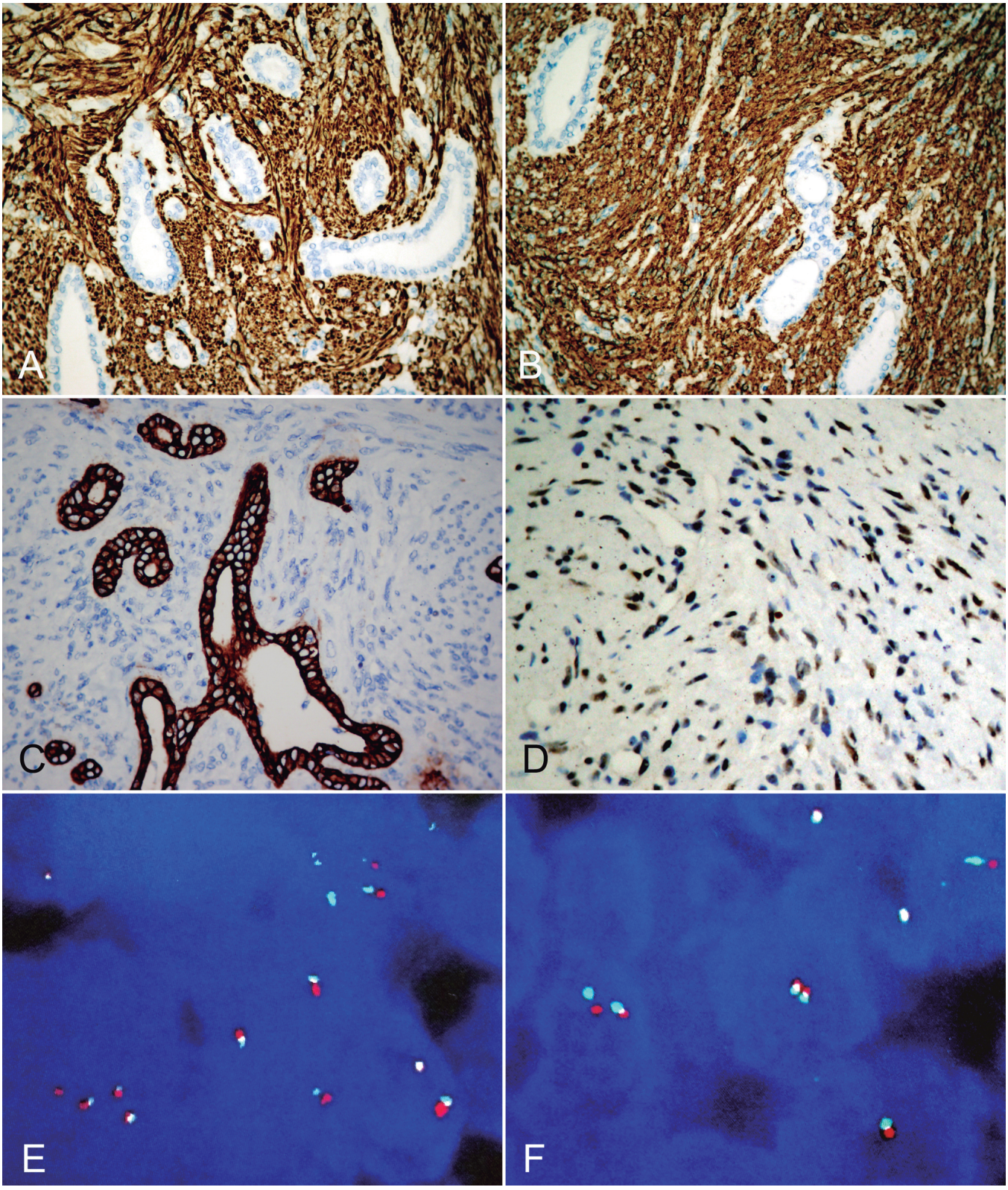

Fig. 4. Immunohistochemical and FISH assay of renal mass. **A.** The spindle cells of tumor were diffusely immuno-positive for Desmin and smooth muscle actin **(B). C.** The epithelial tubules were positive for pan-cytokeratin (AE1/AE3). **D.** Spindle cells component showed focal immuno-positivity for estrogen receptor (ER). **E.** By FISH assay, there was neither ETV6 nor SYT **(F)** gene fusion detected in the tumor. A-D, immunohistochemical staining; E-F, FISH assay. × 400.

recurrence of tumor and no lymph node or distant metastasis during this period.

Discussion

Mixed epithelial and stromal tumor of kidney (MESTK) is a rare, distinct entity of renal neoplasm, firstly termed by Michal and Syrucek in 1998 (Michal and Syrucek, 1998). However, other tumors under different names applied in the literature, such as "leiomyomatous hamartoma" by Block NL in 1973 (Block et al., 1973), "adult variant of congenital mesoblastic nephroma" by Trillo in 1990 (Trillo et al., 1990), "mesoblastic nephroma of adulthood" by Durham in 1993 (Durham et al., 1993), "cystic hamartoma of the renal pelvis" by Pawade in 1993 (Pawade et al., 1993), "adult mesoblastic nephroma" by Truong in 1998 (Truong et al., 1998), also share the similar histological features of MESTK and indeed are real MESTKs. Therefore, in 2004, WHO classification of tumors of urinary system and male genital organs accepted MESTK as a rare entity, and suggested ''MEST'' could be a more appropriate descriptive term because it "best captures the tumor nature" (Eble, 2004). In 2016, the latest edition of WHO classification encompasses adult cystic nephroma and MESTK as "MEST family" on the basis of similar age and sex distribution, as well as similar immunohistochemical profile and overlapping histological features (Antic et al., 2006; Michal et al., 2016).

Although MESTK was initially recognized as a benign tumor by Michal and Syrucek and his colleagues (Michal and Syrucek, 1998), and most reported cases displayed their bland histological characteristics and benign clinical course, recently a few cases of malignant form of MESTK have been reported in the literature. We have reviewed only 12 bona fide cases reported as malignant MESTK, it revealed that the features of malignancy in all cases could be observed in either epithelial or spindle cell components, accompanied by aggressive behavior and rapid lethal course (Table 1). In 2008, Jung et al. proposed several clinicopathological criteria for malignant MESTK, including (i) tumor location-the epicenter of the tumor should be in the kidney; (ii) 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; (iii) morphologically malignant components should be intimately associated with benign counterparts; (iv) primary renal sarcoma or metastasis should be ruled out. In the present case, however, we did not find any malignant histological features of tumor, except for its central location in the kidney. According to the Jung's criteria, our case did not meet the malignant MESTK. However, unlike previously reported benign MESTKs, our case was characterized by its unexpected finding of renal venous involvement. To our knowledge, this is the first case of MESTK with renal vein extension, but without striking histological atypia of both elements of the tumor, and high mitotic figures or

Table 1. The clinicopathological characteristics of malignant MESTKs described in previous reports.

No.	Author (yr.)	Age (yrs.)/ Gender	Location / Size (cm)	Invade site	Malignant component	Treatment	Outcome
1	Svec et al., 2001	46/ Female	Upper pole / 7.0	Perirenal invasion	Stroma (synovial sarcoma like)	RT and CT	Died at 17 months follow-up
2	Bisceglia and Bacchi, 2003	24/ Female	Hilar region/ 6.5	NA	Stroma (synovial sarcoma like)	NA	NA
3	Nakagawa et al., 2004	43/ Female	Hilar region/ 7.0	Hilar fat invasion	Stroma (unclassified sarcoma)	NA	Died at 43 months follow-up
4	Nakagawa et al., 2004	31/ Female	NA/ 7.0	Capsular invasion	Stroma (unclassified sarcoma)	NA	Died at 11 months follow-up
5	Yap et al., 2004	53/ Female	Upper pole / 26.0	Perirenal invasion	Stroma (unclassified sarcoma)	RT and CT	Died at 9 months follow-up
6	Sukov et al., 2007	84/ Female	NA/ 10.5	Confined to kidney	Stroma (sarcoma with rhabdoid feature)	RN	NED at 17 months follow-up, alive
7	Jung et al., 2008	53/ Female	Middle region/ 13.0	Perirenal invasion	Stroma (unclassified sarcoma)	CT	NED at 8 months follow-up, alive
8	Jung et al., 2008	56/ Female	Upper pole/ 6.0	Confined to kidney	Stroma (sarcoma with heterologous component)	RT	NED at 36 months follow-up, alive
9	Kuroda et al., 2008	54/ Female	Upper pole / 7.6	Systemic metastases	Epithelium and stroma (carcinosarcoma like)	RN	Died 5 months after surgery
10	Suzuki et al., 2013	67/ Male	Lower region/ 3.5	Confined to kidney	Stroma (undifferentiated sarcoma)	RN	NED at 22 months follow-up, alive
11	Zou et al., 2014	19/ Male	Upper pole/ 28.0	Perirenal fat and right live invasion	Stroma (undifferentiated sarcoma)	RN and RT	Recurrence at 9 months follow-up, alive
12	Mudaliar et al., 2014	75/ Female	Hilar region/ 8.1	Confined to kidney	Epithelium (papillary renal cell carcinoma)	RN	NED at 10 months follow-up, alive
13	Present case	50/ Female	Central region/ 3.5	Renal vein extension	Benign histological appearance	RN	NED at 16 months follow-up, alive

RT, radiotherapy; CT, chemotherapy; NA, not available; RN, radical nephrectomy; NED, no evidence of disease.

proliferative index. We have compared the histological difference between the mass in renal pelvic cavity and the intravenous mass in the present case, and tried to establish the histological prognostic indicators of MESTK with renal venous involvement. However, the cytological bland spindle cells and epithelial component were observed in both masses. Neither necrosis nor high mitotic activity was found in tumors.

Due to the limited case reports and the short follow-up period, we could not determine the prognosis of MESTK with intravenous involvement. In fact, we are not sure the renal venous involvement of the current case represents a real vascular invasion or a specific growth pattern, just like intravenous leiomyomatosis (IVL) occurring in female uterine (Oliva et al., 2014). In IVL, some researchers suggested that it might derive from a uterine myoma or intrauterine venous wall that has grown and extended intravenously (Fukuyama et al., 2011). In the current case, a slender pedicle was linked between renal and intravenous masses. Therefore, we suggest that intravenous MESTK does not invade the vessel by breaking the venous wall, but rather stretches the vascular wall to extend along the vascular lumen covered with endothelium cells. Unlike the real invasive growth pattern, the intravenous MESTK might free float within the lumen or adhere to the vessel wall. That might be the reason why the intravenous mass was bluntly separated form the wall of renal vein completely at surgery. This vascular extension pattern could be also found even in renal cell carcinomas, which often extend into veins surrounded by an endothelial layer with a discrete, rounded tumor thrombus (Sugino et al., 2004). In fact, renal oncocytoma has also been reported to occasionally invade veins or vein branches (Hes et al., 2008), it does not appear to have an adverse effect on the benign behavior of oncocytoma. Similarly, there are reports of angiomyolipoma with renal vein and caval tumor thrombus. Therefore, we postulate that MESTK with vein involvement still behaves in a benign fashion if cytologically malignant features are absent. Of course, additional studies of MESTK with vein involvement will be needed to determine whether this imparts any adverse behavior.

Although a few cases of MESTK showed specific genetic alteration, including translocation t (1; 19) (Compérat et al., 2005), the histogenesis of this tumor is unknown. The female preponderance of MESTK, combined with the frequent expression of ER and PR in the stromal spindle cells, suggest that hormones might play a role in the evolution of this tumor (Michal et al., 2004). However, ER and PR expression are not by themselves diagnostic of MESTK, and characteristic morphological features should take precedence (Mohanty et al., 2009). Due to its rarity, the microscopic morphological appearances of mixture of epithelial and spindle cell components in MESTKs may pose a diagnostic dilemma. The major differential diagnosis of benign form of MESTKs includes cystic nephroma (CN), congenital mesoblastic nephroma (CMN), angiomyolipoma with epithelial cyst, and recently described smooth muscle and adenoma-like renal tumor (SMART). There are two types of CN in kidney, paediatric and adult CN. There are striking similarities between adult CN and MESTK in morphological, immunohistochemical and clinical characteristics. In 2016 WHO classification of tumors of urinary system, a new entity of "mixed epithelial and stromal tumor family" has encompassed adult CN and MESTK (Michal et al., 2016). However, paediatric CN is a multilocular, exclusively cystic neoplasm of very young children, in which the septa contain only fibrous tissue and differentiated tubules. There is no ovarian-type stroma present in the septa of tumor (Argani et al., 2016). Genetically, most paediatric CN harbour *DICER1* mutations, but the fact is that these mutations have not been found in other tumors. The adult CN and MESTK are not related to paediatric CN. Hence, a renal cystic tumor occurring in infant or early childhood without ovarian-type stroma may support the diagnosis of paediatric CN. CMN is generally a solid mass composed of uniform spindle stromal cell components with specific genetic alteration of *ETV6-NTRK3* gene fusion in cellular CMN (Argani and Sorensen, 2004). Unlike MESTK, CMN can entrap islands of renal tubules and is infiltrative at its interface with renal parenchyma. In our case, however, tumor was well circumscribed and lacked the *ETV6* rearrangement, which was not consistent with the diagnostic criteria of CMN. Angiomyolipoma with epithelial cyst is a variant of angiomyolipoma characterized by mixed, solid, and cystic architecture, with the cysts lined by cuboidal to hobnail epithelial cells. These epithelial cysts are thought to be entrapped renal tubular epithelium with immuno-positivity of cytokeratin, PAX2 and PAX8. There is also a compact subepithelial cambium-like layer of stroma cells with immuno-positivity of ER and PR, which is thought to be a manifestation of Müllerian differentiation of perivascular epithelioid cells (Martignoni et al., 2016). These histological and immunohistochemical appearances of angiomyolipoma with epithelial cyst mimic MESTK. However, the presence of mature fat, thick-wall blood vessels, and co-expression of melanocytic and smooth muscle markers, including HMB45, melan A, Cathepsin K and smooth muscle actin, in myoid-appearing cells support the diagnosis of angiomyolipoma. SMART has been recently described and termed as biphasic renal neoplasm by Smith NE and his colleagues in 2015. It was characterized by predominance of smooth muscle and epithelial nodules without ovarian-like stroma and ER labeling (Smith et al., 2015). Unlike MESTK, SMART lacks clinical history of hormone exposure, which suggests it may represent a distinct entity. The authors believe that there are some differences between SMART and MESTK, and favor SMART as a distinctive entity. However, if SMART is, in fact, part of the spectrum of MESTK, all of its distinct features "would expand the currently reported characteristics of MESTK" (Smith et al., 2015).

For the malignant form of MESTK, the major differential diagnosis includes primary renal synovial sarcoma, primary renal sarcoma and renal cell carcinoma with sarcomatoid change. Renal synovial sarcomas show some features observed in MESTKs, such as monomorphic plump spindle cells and entrapped native renal tubules, which are lined by CK-positive hobnail epithelium. However, the ovarian-like stroma and immuno-positivity for expression of ER is a distinctive feature of MESTKs and is not observed in synovial sarcoma. More importantly, synovial sarcoma shows *SYT-SSX* gene fusion, which is not detected in MESTKs, which can help differentiate it from MESTKs. In previously reported malignant MESTKs, two cases showed synovial sarcoma like stroma without molecular analysis (Svec et al., 2001; Bisceglia et al., 2003). It should be clarified if they were indeed synovial sarcoma of kidney by FISH assay for *SYT-SSX* gene fusion. Renal sarcomas also tend to entrap existing renal tubules and form cystic structures, which exhibit a similar appearance to malignant MESTKs. However, ER-positive ovarian stroma in MESTKs would help differentiate these 2 lesions. Sarcomatoid change occurs in approximately 5% of all renal cell carcinoma, appearing malignant fibrous histiocytoma-like or fibrosarcoma-like features. Identification of a well-defined histologic type of renal cell carcinoma in the background of sarcomatoid change allows a definitive diagnosis.

In conclusion, although most MESTKs have behaved in a benign fashion following surgical excision, recurrence and malignant transformation can occur in rare cases with dismal prognosis. We reported herein the first case of MESTK with renal venous involvement. We prefer to label MESTK with renal vein extension lacking cytological malignancy as a benign renal tumor. However, this postulate should be substantiated by further more studies with a long-term follow-up.

Conflict of interest. The authors declare that we have no competing interests.

Authors' contributions. WLX and JYL made contributions to acquisition of clinical data, and analysis of the histological features by H&E staining and immunoassays. They were joint first co-authors and made an equal contribution to this work. BL carried out the immunohistochemical staining. XYT carried out the FISH assay. ZL revised manuscript critically for important intellectual content and had given final approval of the version to be published. All authors read and approved the final manuscript.

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