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A rare case of Mixed Malignant Epithelial & Stromal tumor of Kidney: Diagnostic approach with review of literature.

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Abstract

Mixed epithelial & stromal tumor kidney (MESTK) is a rare kidney neoplasm. Majority of cases of MESTK behave in a benign fashion. Very few cases of malignant MESTK have been reported in literature, but with only one malignant component i.e., in either epithelial or stromal component. We report a case of malignant MESTK with malignancy in both epithelial & stromal components in a 30-year-old male patient who presented with complaints of painless hematuria with passage of clots for last 6 months, acute left flank pain and enlarging mass in the upper abdomen. Ultrasound (USG) and contrast enhanced computed tomography (CECT) abdomen showed a large well-defined mass seen arising from upper half of left kidney. Clinically, a provisional diagnosis of renal cell carcinoma (RCC) was made. Left radical nephrectomy was done. A definitive diagnosis of malignant MESTK with papillary renal cell carcinoma and fibrosarcoma was made based on the detailed histopathological and immunohistochemical examination.

Keywords: Solid-Cystic, Renal Mass, Malignant Transformation, Stromal Tumor, IHC.

Introduction

Malignant mixed epithelial & stromal tumor of kidney (MESTK) is a rare biphasic renal tumor comprising of both the epithelial and stromal components. Majority of cases behave in a benign manner.

The classification of renal tumor has shown a tremendous change in its classification with incorporation of few newer entities like translocation RCC, tubular mucinous and spindle cell carcinoma, familial RCC and MESTK. MESTK is usually seen in perimenopausal female. This entity was first described Miceral & Syrucek and Adsay

et al in the year 1998.[1] Till date approximately 100 cases have been reported, however, majority are benign.[2-6] But, till date, only 13 cases of malignant MESTK are reported in literature.[5-14] We report a case of solid-cystic renal neoplasm which was clinically diagnosed as RCC, however, on extensive grossing and sectioning, a diagnosis of MESTK with malignancy in both the epithelial and stromal components was made as papillary RCC and fibrosarcoma along with their benign epithelial and stromal component.

Case Report

A 30-year-old male presented to hospital with complaints of off and on painless hematuria for last 6 months with passage of clots. He also had burning micturition, left flank pain, which was acute in onset and radiated to abdomen. The patient had recently noticed an enlarging mass on left upper abdomen. Per abdominal examination revealed the presence of lump of size 20x15 cm in left lumbar region, which was non-tender, mobile, hard and bimanually palpable. His basic blood investigations and biochemical parameters were within normal limits. Routine urine examination showed pus cells (2-4/HPF) and red blood cells (15-20/HPF). However, urine culture was sterile.

Radiological investigations were done. USG abdomen showed a large well-defined heterogenous shadow, measuring 14.6x13 cm seen arising from upper half of the left kidney. CECT chest and abdomen was done which confirmed a large mass arising from left kidney measuring 10.5x19x21 cms [Figure 1A-B]. Superiorly, the mass was seen compressing spleen, splenic vessels, stomach, body of pancreas with indistinct fat planes between mass. Laterally the mass crossed midline and was seen displacing the small bowel loop. Mass was also seen abutting anterior, lateral and uncinate process of pancreas. Based on the clinical and radiological findings, a provisional diagnosis of renal cell carcinoma was made.

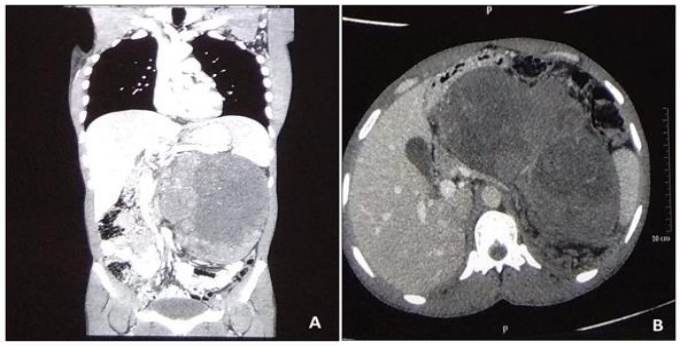

Figure 1A-B: CECT chest & abdomen showing a large mass arising from left kidney, measuring 21x19x10.5 CMS

Left nephrectomy was done for the patient and sent for histopathological examination. On gross findings, the specimen measured 23x16x12 cms [Figure 2A-B]. Cut section showed a large variegated tumor replacing the entire renal parenchyma. Tumor was soft to firm, grey-white to dark- brown with foci of greyish white and yellowish areas [Figure 3A-B]. Extensive grossing and sectioning were done from different areas of the tumor. Sections were stained with hematoxyline and eosin (H&E) stain.

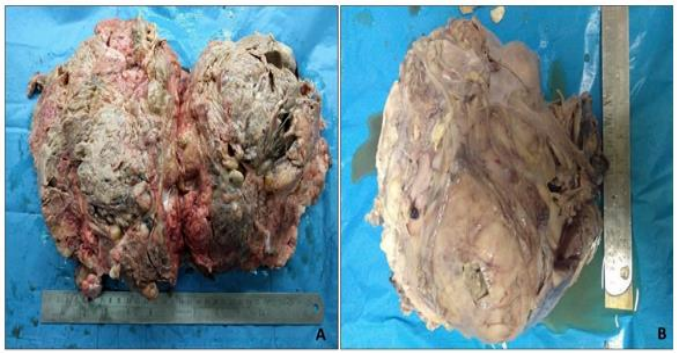

Figure 2A-B: Left radical nephrectomy specimen measuring 23x16x12 CMS [A- Unfixed, B-Formalin Fixed]

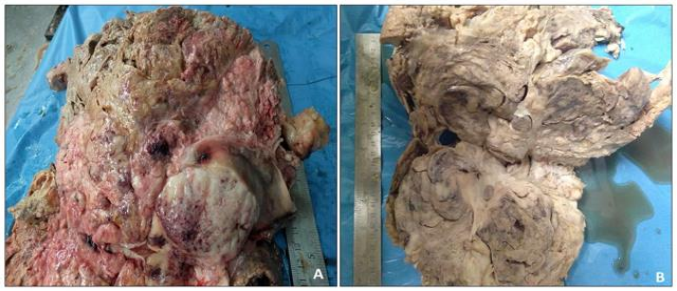

Figure 3A-B: Cut section showing a large tumor with variegated appearance replacing the entire renal parenchyma [A- Unfixed; B- Formalin Fixed]

Multiple sections showed a composite tumor with epithelial and stromal components [Figure 4A]. There was proliferation of bland looking spindle cells which resembled phylloides tumor with stromal hyperplasia and leaf-like clefting with interspersed benign tubules [Figure 4B]. The benign tubal epithelium showed hobnail appearance [Figure 4C-D].

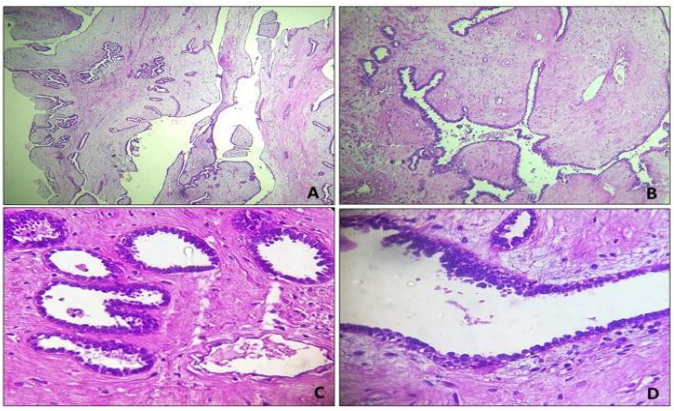

Figure 4A-D: A-Section showing a composite tumor with epithelial and stromal components [H&E, 20X]; B & C-Proliferation of bland looking spindle cells resembling phylloides tumor with stromal hyperplasia & leaf-like clefting with interspersed benign tubules [H&E, B-20X, C-40X]; D- Benign tubal epithelium showing hobnail appearance [H&E, 40X].

Along with above mentioned benign epithelial & stromal component, also noted were malignant neoplastic comprising of approximately 70% of total neoplastic mass [Figure 5A]. These cells showed mild to moderate pleomorphism with high nucleo-cytoplasmic ratio, vesicular chromatin and inconspicuous to conspicuous nucleoli and scattered mitotic figures [Figure 5B]. Extensive area of necrosis was noted intermingled with malignant epithelial cells [Figure 5C]. Sections examined also showed epithelial elements with associated stromal cuffing [Figure 5D].

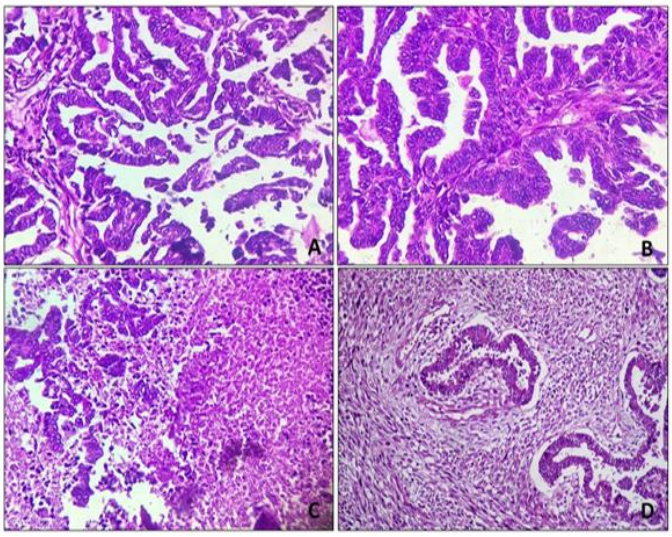

Figure 5A-D: A&B- Malignant epithelial cells arranged in papillae, micropapillae & cells showing mild pleomorphism, high N/C ratio, inconspicuous nucleoli, mitosis [H&E, A-20X, B-40X]; C-Malignant epithelial cells with extensive areas of necrosis [H&E, 20X]; D-Epithelial elements with associated stromal cuffing [H&E, 20X].

Apart from the malignant epithelial cells, also noted were malignant stromal cells arranged in herring bone pattern [Figure 6A]. Cells showed moderate to marked pleomorphic spindled to oval cells with hyperchromatic nuclei, brisk mitosis, and large areas of necrosis [Figure 6B-C]. A single lymph node was isolated and showed evidence of metastasis [Figure 6D]. Focal areas of squamous epithelium with keratinization were noted [Figure7A-B]. Sections from ureter and adrenal were free of tumor [Figure 7C-D].

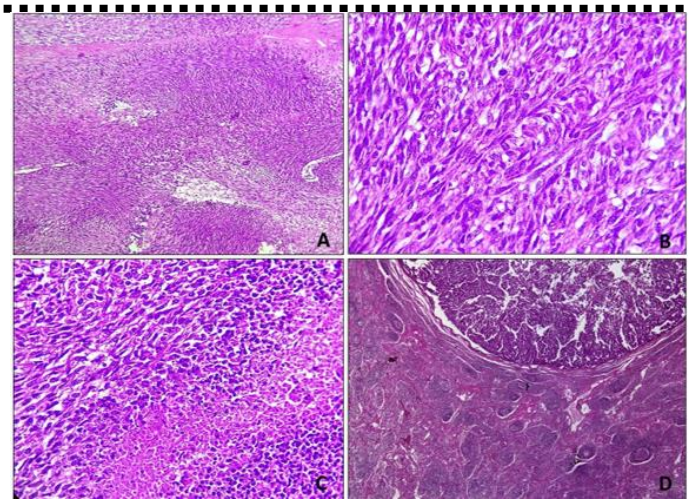

Figure 6A-D: A- Malignant stromal cells arranged in a herring bone pattern [H&E, 10X]; B&C- Malignant stromal component showing pleomorphic spindled to oval cells with brisk mitosis and large areas of necrosis [H&E, B&C- 40X]; D- Section from lymph node showing metastasis [H&E

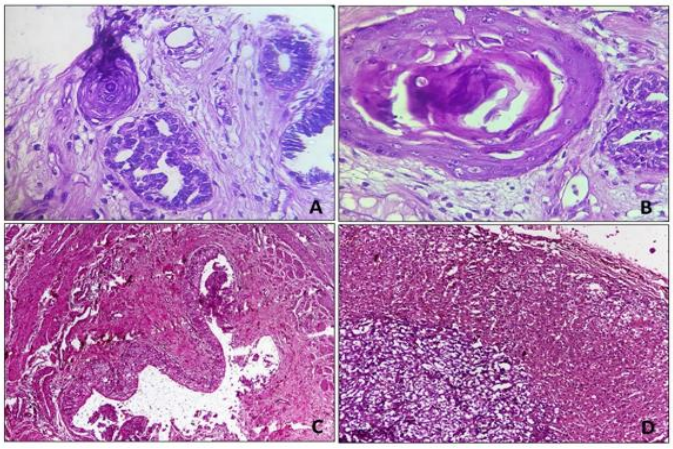

Figure 7A-D: A&B- Focal areas showing squamous epithelium with keratinization [H&E, A-20X, B-40X]; C&D- Sections from ureter & adrenal did not show any tumor deposits [H&E, C&D- 20X]

Based on histomorphology, differential diagnosis which were considered were: 1) Sarcomatoid RCC, 2) Malignant MESTK, 3) Adult wilm's tumour, 4) Primary renal synovial sarcoma. An extensive IHC panel was done to rule out the above-mentioned differential diagnosis, thereby, arriving at a correct diagnosis (Table No. 1).

The immunohistochemistry features of our case are summarized in the Table No. 1:

Positive IHC	Negative IHC
Vimentin: In both epithelial & stromal component.	• WT1 • CD56 • CD99 • p53 • SMA • Desmin • S100 • Bcl2
CK7 & AE1/AE3, CD10, CD15 & EMA: Only in epithelial component.	
Ki67: 60-70%.	

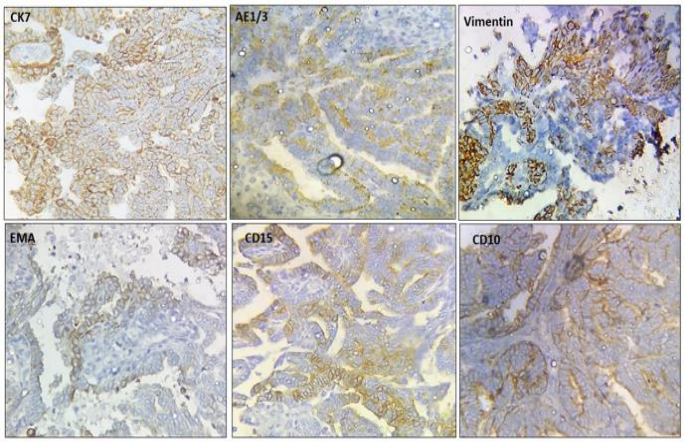

Figure 8: Image showing positivity for CK7 [20X], AE1/3 [20X], Vimentin [20X], EMA [20X], CD15 [20X], CD10 [20X] in epithelial component.

Based on detailed histopathological & immunohistochemical evaluation, a final diagnosis of "Carcinosarcoma of Kidney/ Malignant Mixed epithelial & stromal tumour (Papillary renal cell carcinoma & Fibrosarcoma) of Kidney" [pt3pn1pmx] was made.

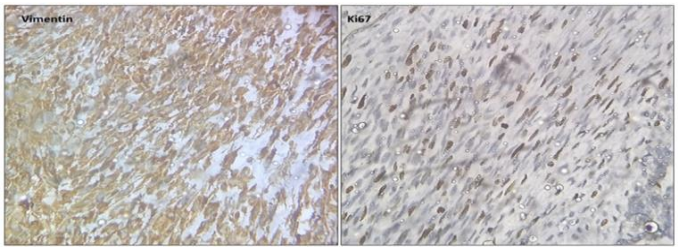

Figure 9: IHC images showing positivity for Vimentin [40X] & Ki67 [40X]

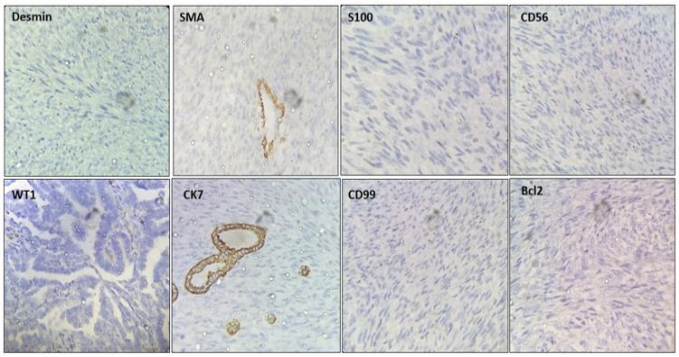

Figure 10: IHC images showing negativity for Desmin, SMA, S100, CD56, WT1, CK7, CD99, Bcl2 [20X].

Discussion

MESTK is a rare and recently recognized neoplasm of unknown histogenesis that consists of both epithelial and stromal cells. This entity was reported for the first time by Michael & Syrucek in 1998.[1] This was previously labelled as cystic hamartoma of the renal pelvis, adult type of mesoblastic nephroma or cystic nephroma. In 2004, WHO adopted the MESTK as an official entity with solid and cystic architecture.[4-6]

A strong female preponderance is noted in cases of MESTK with ratio of 6:1, which very well explain the hormonal basis in its histogenesis. It is usually seen in the perimenopausal women with mean age being 48 years.[7-9]

It has been seen mostly in peri-menopausal to older women. This implies that a disturbed hormonal environment contributes to the pathogenesis of MESTK; however, no correlation between estrogen therapy and MESTK has been established. Hence, association of MESTK with estrogen warrants further study.[6-10]

This tumour usually consists of epithelial component composed of cuboidal or columnar cells along with spindle stromal cells including smooth muscle cells and ovarian-like parenchyma. Few reports also explain the differentiation of these epithelial & stromal cells from a common progenitor cell.[6-7] A resemblance with structure like uterine cervix, fallopian tube epithelium, or colonic epithelium have also been noted. IHC help in confirming the presence of both components with positivity for cytokeratin in epithelial cells and Vimentin along with desmin, SMA, ER & PR in stromal cells. A study reported positive expression of ER in 62% and PR in 85% cases of benign MESTK. ER & PR expression are not usually reported in malignant cases of MESTK, however, in a study by Jung et al,[8] only focal PR positivity was seen in ovarian type of stroma of the benign areas. Our case also did not reveal positivity for ER or PR.

Usually, the cases of MESTK behave in a benign manner. Very few cases of malignant MESTK have been reported in literature [Table no 3]. The size of tumours is larger in malignant cases with average size being 10.4 cm (range; 6-26 cms) as compared to the benign counterpart with average size being 6.7cms (range being 1-14 cm). Malignant cases showed gross areas of haemorrhage & necrosis. In malignant cases of MESTK, malignant component is noted only in single component, i.e., epithelial or stromal. Our case is much rarer in having malignant components in both epithelial & stromal components. Jung et al[8] rereported 2 cases of MESTK with sarcomatous transformation, in which one case showed divergent heterologous differentiation with rhabdomyosarcomatous & chondrosarcomatous areas.

Jung et al[8] described the following criteria in order to make diagnosis of malignant transformation in cases of MESTK: a) The epicenter should be in the kidney, b) There should be a clear cut evidence of benign epithelial & stromal components with tubules or cysts lined by bland epithelial cells and spindle cell stroma resembling that of ovarian type of parenchyma, c) Histologically, the malignant components should be intimately associated with their benign counterparts, and d) Any evidence of primary renal sarcoma or any metastasis should be ruled

out. Hence, an extensive grossing and sectioning is required from different areas of the gross specimen to have MESTK with evidence of malignant transformation. Before arriving at a definitive diagnosis, various differential diagnosis like sarcomatoid renal cell carcinoma, leiomyosarcoma, synovial cell sarcoma, adult wilm's tumor, etc. should be ruled out. Table 2 summarises the detailed histological and IHC findings of the differentials of malignant MESTK.

These differential diagnoses are described with detailed histological and immunohistochemical features (Table 2).

Features	Sarcomatoid RCC	Malignant MEST	Primary renal sarcoma (NOS)	Adult Wilm's
Histological Features	Seen in 5% of RCC. Intermingled carcinomatous & sarcomatous component (+) No benign epith & stromal areas.	Composite tumor. Benign & Malignant epithelial & stromal elements.	Distinct hemangiopericytoma like vascular pattern. In biphasic: epithelial cells more cuboidal & polygonal. No prominent subepithelial condensation of stroma. No typical benign mixed epithelial tumor to prove malignant transformation.	Triphasic pattern: blastemal, stromal & epithelial Elements.
IHC features	CK7&AE1/3 (+) in sarcomatous area. Epith markers +ve in even undiff sarcomatoid RCC, with no epithcomp.	Epithelial: C/K7, AE1/3, EMA, CD15, CD10, Vimentin Stromal: SMA/ Desmin, Myogenin, Bcl2, S100	Bcl2, vimentin, CD99, CD56, EMA.	CD56, CD57 & WT-1

Suzuki et al[13] noted the first male patient with malignant MESTK in their series of 8 cases of malignant MESTK. But, in their case, malignancy was noted in only one component, i.e., stromal component. We present the first case of malignant MESTK in a male with malignancy in both the components along with well-defined benign counterparts in both epithelial and stromal elements. Majority of the cases of MESTK show cystic and tubular structures lined by a low cuboidal epithelium with areas of hobnail-type of epithelial cells with eosinophilic cytoplasm.[12-15] Spindle cell stroma of MESTK typically contains at least focal areas with an ovarian like-appearance and expression of ER/PR (focal). This hormonal receptor expression by ovarian like stroma along with female preponderance, suggest a hormonal basis in its pathogenesis. Our patient was referred to higher oncology centre after the diagnosis of malignant MESTK was made on histopathology for further management.

Table 3: Shows an extensive review of literature highlighting all the cases of malignant MESTK reported till date in literature along with the features in index case.

Authors	Sex	Age (y)	Size (cm)	Location	Extension	Sarcomatous component	Epithelial component	Postop treatment	Follow up (MThs)	Status
Svec et al[2] (2001)	F	46	7.0	Upper pole	Perirenal extension	Undiff (SS) like	-----	RT, chemo	Chemo, RT17	Died
Bisceglia & Bacchiet[3] al (2003)	F	24	6.5	Hilar region	Unspecified	SS like	-----	Unknown	Unknown	Unknown
Nakagawa et al[5] (2004)	2 F	43/31	7/7	Hilar region (1) Unspecified (1)	Hilar fat/ capsular incvasion	Unclass sarcoma	-----	None	43/11	Both died

Yap et al[10] (2004)	F	53	26	Upper pole (1)	Perirenal invasion	--do--	-----	Chemo, RT	9	Died
Sukov et al[6] (2008)	F	84	9	Upper pole	Unspecified	RMS	----			
S.J. Jung et al[8] (2008)	2 F	53/56	13/6	Middle aspect (1) Upper pole (1)	Perirenal/ confined to kidney	Unclass sarcoma (1) Heterologous sarcoma (1)	-----	Chemo/ RT	8/36	Alive without disease
Kuroda et al[7] (2008)	F	54	7.6	Upper pole	Unspecified	Undiff sarcoma, chondrosarcoma, RMS	Adenocarcinoma with endometroid	Chemo, RT	Unknown	Unknown
Suzuki et al[13] (2013)	M	67	3.5	Lower pole	Unspecified	Undiff sarcoma	-----	Chemo, RT	22	Alive without disease
Zou et al[14] (2014)	M	19	28	Upper pole	Unspecified	Undiff sarcoma	-----	Chemo, RT	9	Recurrence & Mets
Bakavicius et al[15] (2018)	F	31	6	Upper pole	Invading IVC	Malignant spindle cell	-----	Chemo, RT	12	Recurrence & Mets
Present case	M	30	16	Upper pole	Perinephric fat, capsule, hilum	Fibrosarcoma	Papillary RCC	Chemo, RT	05	Alive without disease

Conclusion

To summarize, we present a rare case of malignant MESTK on histopathology. To the best of our knowledge, this is the first case to be reported in literature in a male patient with malignant transformation in both, the epithelial as well as the stromal components. However, due to the paucity of cases and only few being reported in literature, the exact pathogenesis and clinical behavior as well as the prognosis of this rare malignant neoplasm, further studies are awaited on a greater number of cases.

The index case reiterates the importance of extensive grossing and sectioning along with detailed histopathological and immunohistochemical evaluation to arrive at a correct diagnosis of such rare entity.

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