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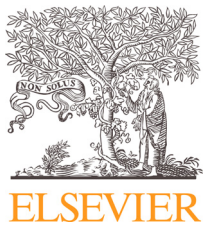

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Case Report

Role of imaging in the diagnosis and management of mixed epithelial and stromal tumors of the kidney: Case series and comprehensive review ☆,☆☆

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ABSTRACT

Mixed epithelial and stromal tumor (MEST) of the kidney is a rare benign neoplasm composed of both stromal and epithelial components. MEST is mainly seen in adults with a strong predilection for perimenopausal women with history of hormone replacement therapy. While MEST is generally benign, there are reported cases of malignant transformation and adverse clinical outcomes. This case series will present 7 cases of this rare renal neoplasm with emphasis on radiological imaging as an important tool in the guidance of clinical management. Considering the rarity of this tumor and its variable presentation, understanding the radiological features on multiple modalities can guide appropriate clinical and surgical management of MEST patients.

Introduction

Mixed epithelial and stromal tumor (MEST) of the kidney are uncommon benign tumors with increased incidence in perimenopausal women and an estimated female to male ratio ranging between 6:1 and 37:2 in various literature [1–3]. This neoplasm was first described in 1973 under various names and was later termed "mixed epithelial and stromal tumor" by Michal and Syrucek in 1998 [2,4]. Epidemiological data is limited which reflects the rarity of MEST, with approximately 100 individual published case reports and small case series [5]. Histologically, MEST of the kidney can be composed of both cystic and solid elements with variable cystic to solid ratio. The solid component is further subdivided by a biphasic growth pattern of stromal and epithelial cells [4]. There is variable cystic to solid ratio within the architecture and variable cellularity within the spindle cell component of the solid

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areas [6]. Considering the spectrum of histological and morphological features, these tumors have been identified under various names due to the variable histopathological features identified in a small number of case studies. However, in the recent 2022 WHO update on classification of renal neoplasms, the distinct term "mixed epithelial and stromal tumor family" now includes both MEST and Adult Cystic Nephroma (ACN) based on similar histochemical profile, age, and gender distributions [7].

MEST is classically seen in older females with a reported mean age of 49.7 years old [4]. The association between hormone replacement therapy (HRT) and MEST has been anecdotally presented on several case reports [6,8]. However, MEST does not appear to be exclusive with this clinical picture. MEST has been reported both in a female patient who did not have hormone replacement therapy and in a 24-year-old male [6,9].

This tumor is typically detected incidentally or with nonspecific genitourinary symptoms such as hematuria and abdominal pain [2,5,6,10]. When discovered incidentally on imaging, clinicians generally need to consider a wide spectrum of differential diagnosis. However, due to the variability in clinical presentation, clinical findings alone are not sufficient for accurate diagnosis of MEST. Current accepted diagnostic evaluation of MEST begins with appropriate radiological imaging for preoperative diagnosis and surgical planning [5]. Classic computed tomography (CT) appearance of MEST usually consists of a well-circumscribed, heterogenous cystic and solid renal mass with enhancing internal septa and delayed enhancement.[5] Given the rarity of the disease, ultrasound findings are not as well characterized with reports describing a heterogenous hyperechoic mass or a multilocular cystic mass without a vascular solid component [2,11]. On MRI evaluation, the cystic component is usually T2 hyperintense due to fluid intensity, and the solid components are T2 hypointense with mild enhancement depending on the extent of spindle cell involvement [5,12]. Moreover, 34% of MESTs can contain adipose tissue, which can be seen in Angiomyolipoma (AML) of the kidney [5]. Due to its variable appearance, MEST has a number of renal mimics on imaging including multilocular cystic renal cell carcinoma (RCC), multicystic dysplastic kidney, epithelioid AML, AML with epithelial cysts, complex renal cysts, and renal abscesses [5,12]. As such, clinical presentation (i.e. patient sex, symptoms) coupled with specific radiological features (i.e. thickness of internal septa, enhancement of solid components) is critical to narrowing the differential diagnosis.

Histopathological analysis is the current gold standard for definitive diagnosis of MEST [13]. On histology, MEST has a distinct biphasic pattern with both a stromal component and an epithelial component. Stromal cells have great variability and are composed of different cell types ranging from smooth muscle cells to spindle cells. There are also areas of hypervascularity, hypocellular fibrous and edematous areas and interspersed adipocytes. In a large study conducted by Calio et al. it was found that 50 out of 53 cases had a predominant stromal component while only 3 tumors had predominant epithelial components [14]. The epithelial component comprises of a combination of smooth muscle cells, tubulopapillary structures, glands, and cysts, likely reflective of its cytological origin from various renal epithelial tissue types including glomeruli, tubular, and collecting duct.

Since initial identification, there has been a moderate number of case reports and series that have largely focused on the histopathological identification of MEST. Clinical diagnosis of MEST prior to surgical resection or biopsy remains challenging due to variability in clinical presentation and diagnostic features. Therefore, in this article, we will describe the clinical and diagnostic features of this rare kidney neoplasm with emphasis on common radiological features and clinical outcome.

Case presentations

Case 1

A 49-year-old woman with a history of nephrolithiasis and medullary sponge kidney presented with flank pain to our emergency department. CT (Fig. 1) detected a 0.6 cm kidney stone which passed and a large ill-defined lobulated right lower pole kidney lesion measuring 3.6 × 2.8 × 3.7 cm causing localized hydronephrosis. The left kidney also showed a 2.1 cm cystic mass with solid nodular enhancing components suggestive of cystic neoplasm. She then left the hospital and came back for positive blood cultures one week later. A repeat CT at that time showed an interval increase in size of the right lower pole lesion, therefore she underwent ultrasound (Fig. 2) guided percutaneous drainage of the right kidney lesion. The fluid cytology of the drainage taken during the procedure was negative for malignancy.

The right kidney lesion diminished in size with percutaneous drainage and home intravenous antibiotic therapy. One month later, she underwent right ureteroscopy with core biopsy of the right kidney mass which showed chronic inflammation and reactive epithelial and stromal changes, with negative cytology for high grade urothelial carcinoma (Fig. 3).

Differential diagnosis for the 2.1 cm left kidney lesion at this time included MEST, chronic inflammatory mass, upper tract transitional cell carcinoma, and multilocular cystic renal cell carcinoma. One year after initial evaluation, the patient underwent robotic-assisted laparoscopic partial nephrectomy of the left kidney. Histopathological analysis of the surgical specimen showed a 2.3 cm MEST with interstitial fibrosis and mild chronic inflammation. Immunohistochemistry was positive for PAX8, ER and PR. One year after the left partial nephrectomy, follow up CT urography (Fig. 4) found no change to the right lower pole mass; however, a second 2.3 cm complex cystic mass was seen in the upper pole of the right kidney. No recurrence of left-sided MEST was demonstrated on subsequent imaging.

Case 2

A 52-year-old woman with history of rheumatoid arthritis and depression presented to our emergency department with left lower back pain. Abdominal ultrasound and subsequent CT (Fig. 5) demonstrated a complex left renal cyst measuring up to 8.0 cm, occupying the entire interpolar region of the left kid-

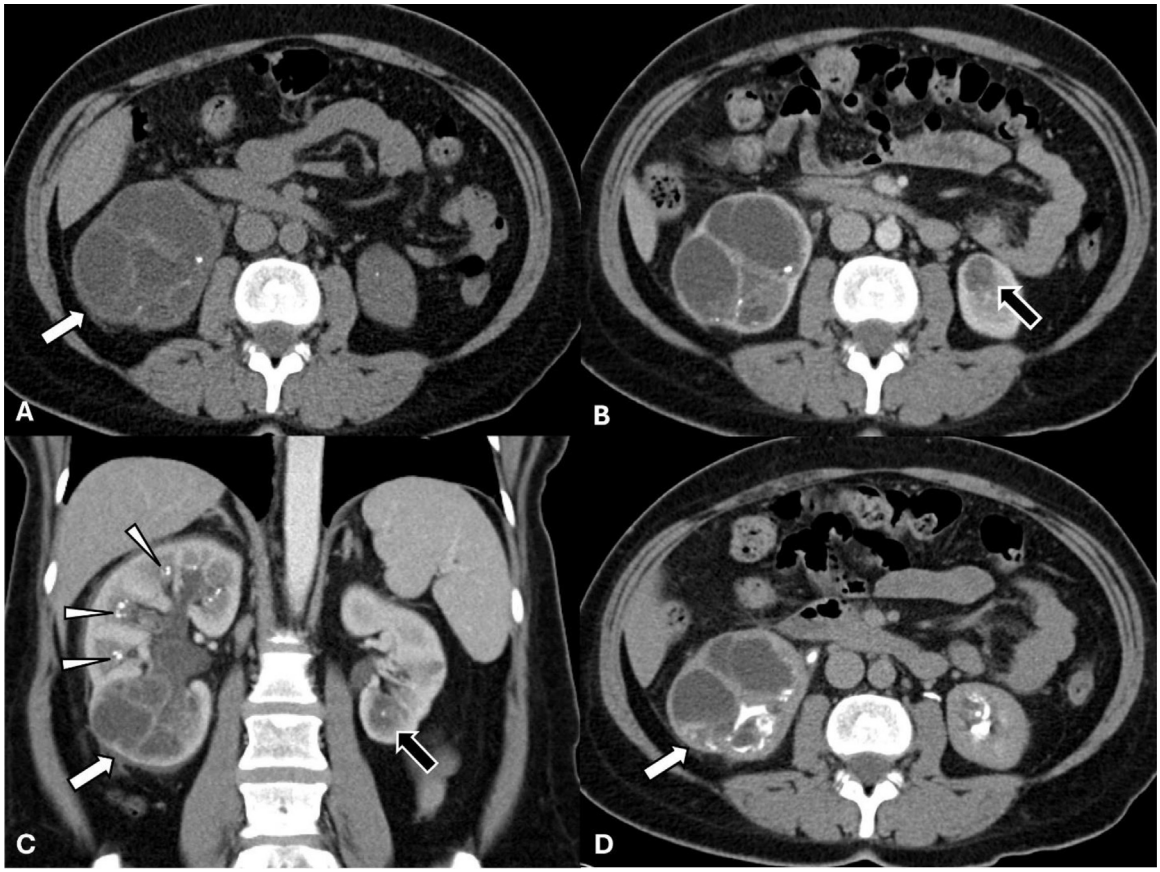

Fig. 1 – Bilateral MEST in a 49-year-old with history of nephrolithiasis and medullary sponge kidney who presented with flank pain. Computer tomography (CT) urogram demonstrated axial unenhanced (A), axial (B) and coronal (C) nephrographic phase contrast-enhanced, and axial excretory phase contrast-enhanced (D) CT demonstrate multiple right nephroliths (arrowheads) and a multiseptated cystic right lower pole structure with calcifications (white arrows). There is mild hydronephrosis due to a distal right ureteral stone (not pictured). Additional hypodensity in the left renal pole (black arrows) with calcification.

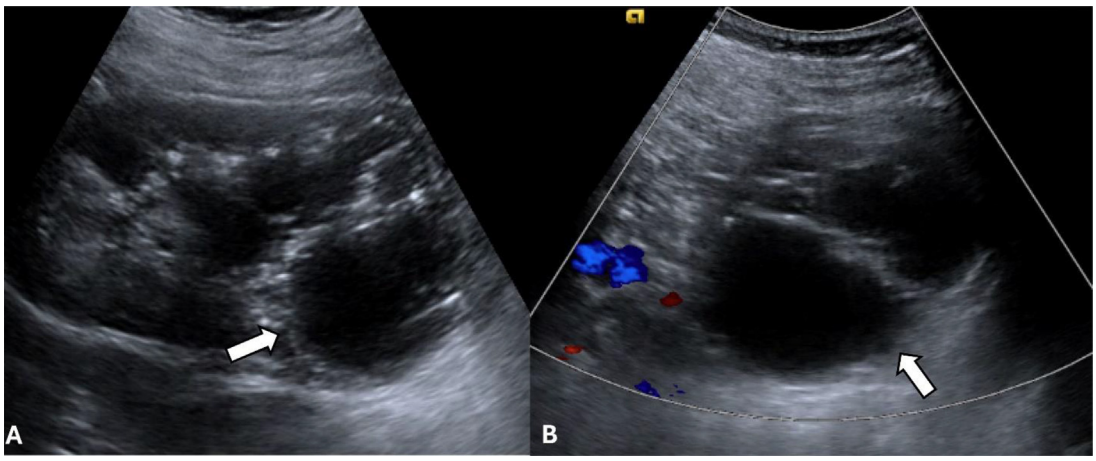

Fig. 2 – Ultrasound of the right kidney with a hypoechoic cystic structure (white arrows) in the lower pole (A). There are no regions of increased vascularity on doppler (B).

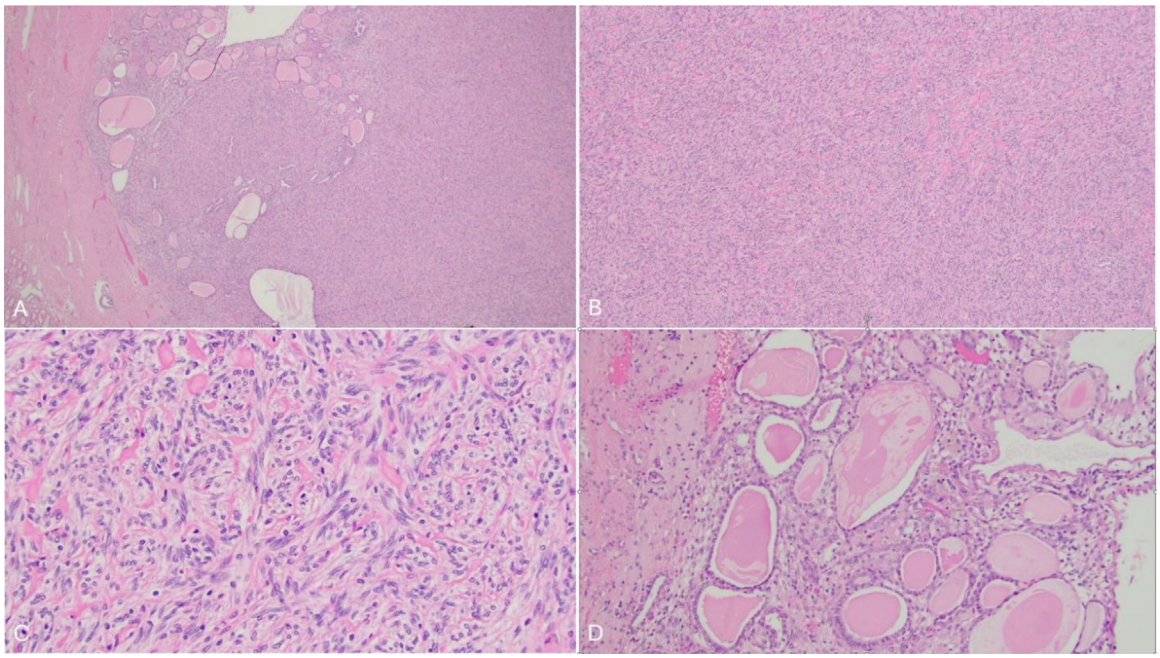

Fig. 3 – (A) Photomicrographs highlight a well circumscribed biphasic tumor involving the renal parenchyma (H&E stain at 20× magnification). (B) The stroma is comprised of ovoid to spindled cells arranged in interlacing fascicles (H&E stain at 40× magnification). (C) The stromal cells are bland, with elongated nuclei, inconspicuous nucleoli, and scant to moderate eosinophilic cytoplasm (H&E stain at 200× magnification). D) The epithelial component consists of tubules lined by cuboidal to low columnar cells with pale cytoplasm and small basally located nuclei (H&E stain at 100× magnification).

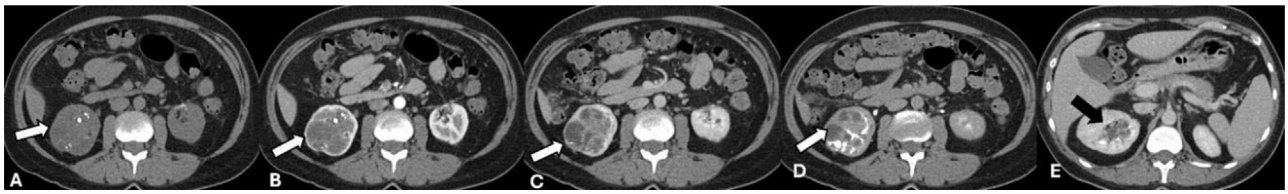

Fig. 4 – Status post left partial nephrectomy with axial unenhanced (A), corticomedullary phase contrast-enhanced (B), nephrographic phase contrast-enhanced (C), and excretory phase contrast-enhanced (D) CT redemonstrating a complex right lower pole structure with thickened septa with delayed contrast enhancement (arrow). Axial nephrographic phase contrast-enhanced (E) CT also shows a new right upper pole cystic structure (black arrow).

ney, with multiple thick enhancing internal septations, classified as Bosniak III. Considering the classification of this lesion, the known malignancy risk at the time was estimated to be between 40% and 50%, therefore she was recommended early surgical intervention.

One month later, the patient underwent laparoscopic adrenal-sparing radical left nephrectomy and incisional hernia repair. Gross examination and histopathological analysis of the left kidney revealed an 8.9 × 6.6 × 3.3 cm hilar MEST, with benign nephrosclerosis and rare intestinal hyaline material. The patient was discharged without any complications and no recurrence has been reported.

Case 3

A 74-year-old woman with history of breast cancer and history of hysterectomy with bilateral salpingo-oophorectomy for endometriosis presented with new microscopic hematuria. She was otherwise asymptomatic, and her breast cancer was treated two years prior with right breast lumpectomy and radiation. She has also been on relevant medical therapy with tamoxifen 20 mg oral once daily. CT (Fig. 6) showed a complex cystic mass in the lower pole of the right kidney measuring 5.0 × 9.0 × 9.0 cm with a thickened rim and enhancing peripheral nodular components. This right complex cystic lesion was classified as Bosniak IV.

Differential diagnosis included cystic renal cell carcinoma. The patient then underwent right laparoscopic partial nephrectomy with an unremarkable postoperative course. Histopathological analysis of the right kidney showed a 11.5 × 10.0 × 3.0 cm MEST with predominantly stromal component and cystic formation. The patient was discharged in stable condition and did not return for additional follow up.

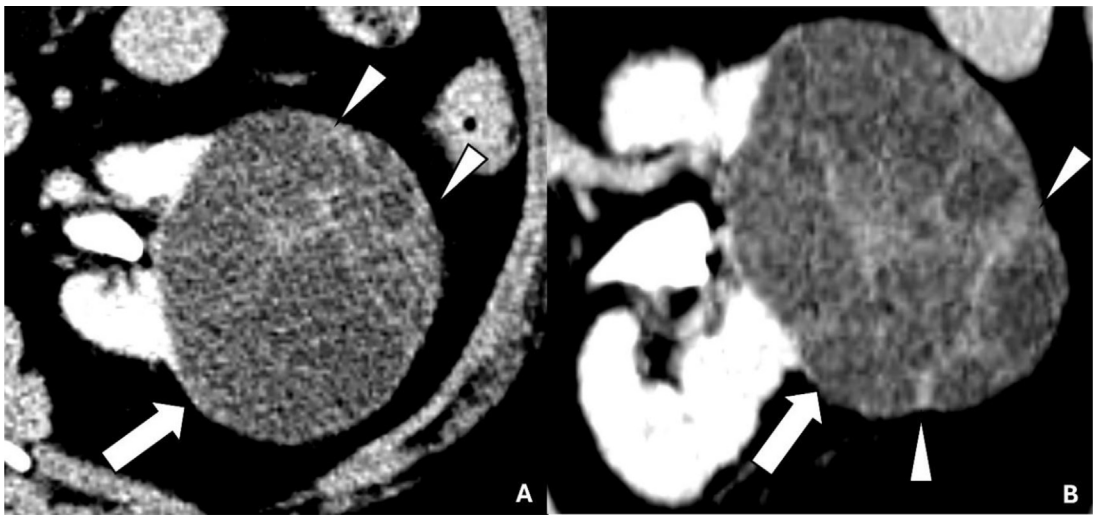

Fig. 5 – MEST in a 52-year-old with lower back pain. Axial (A) and coronal (B) contrast-enhanced CT images demonstrate a complex interpolar left cystic mass (arrows) with thick enhancing internal septa (arrowheads).

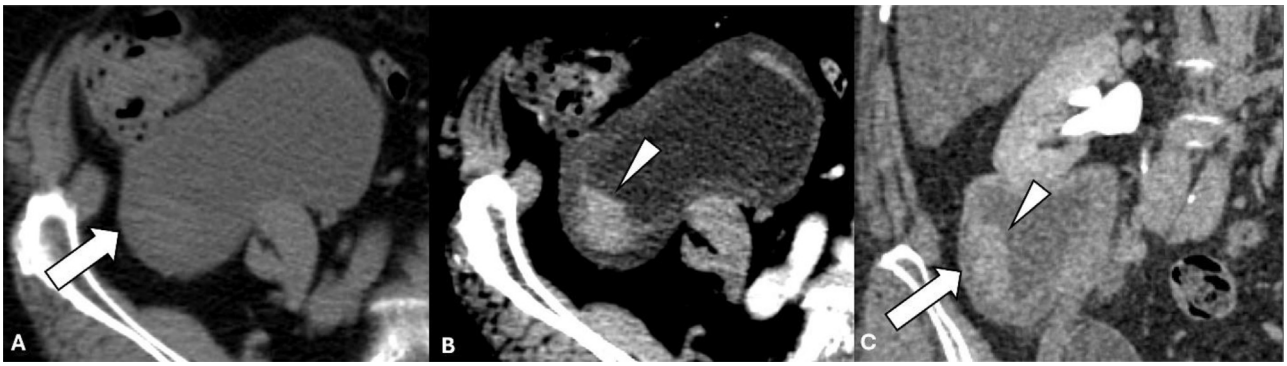

Fig. 6 – MEST in a 74-year-old with microscopic hematuria. Axial unenhanced (A), axial nephrographic phase (B), and coronal (C) excretory phase contrast-enhanced CT scans demonstrate a thick walled exophytic cystic mass (arrows) without internal septations at the right inferior pole with enhancement of peripheral soft tissue nodules (arrowheads).

Case 4

A 51-year-old woman with history of Crohn's disease was incidentally found with a complex left renal cyst on routine imaging. CT (Fig. 7) revealed a stable 7.3 × 4.3 × 4.1 cm lobulated, multiseptated, and partially exophytic cyst in the left renal pelvis. There were no calcifications or nodules seen. Mass effect was demonstrated on the central calyceal system without renal vessel compromise.

The left cystic lesion was classified as Bosniak Type IV. Differential diagnosis included MEST or possible low grade cystic renal neoplasm. She underwent laparoscopic left radical nephrectomy one month later and histopathology revealed a 5.0 × 3.5 × 2.0 cm MEST without parenchymal involvement. There has been no recurrence since her procedure and the patient has remained asymptomatic.

Case 5

A 59-year-old woman with history of hemorrhagic stroke and history of hysterectomy with bilateral salpingo-oophorectomy for a benign uterine mass was incidentally found with a 4.4 cm right renal cyst initially classified as Bosniak IIF. The patient was on medical therapy with estradiol 1 mg orally once daily after her hysterectomy. Active surveillance of this lesion demonstrated stable course until progression was seen on follow up imaging two years later.

CT and MRI (Fig. 8) at this time showed a 8.1 × 7.6 × 6.5 cm complex right renal cyst with interval growth and multiple thin septations. This lesion was classified as Bosniak III. The patient then underwent open radical right nephrectomy with an unremarkable postoperative course. Histopathological analysis of the right kidney specimen showed a large MEST. Follow up imaging four months later did not demonstrate any recurrence.

Case 6

A 61-year-old woman with hypothyroidism and history of prophylactic hysterectomy for vaginal bleeding presented with two days of acute flank pain and left abdominal bulge for two

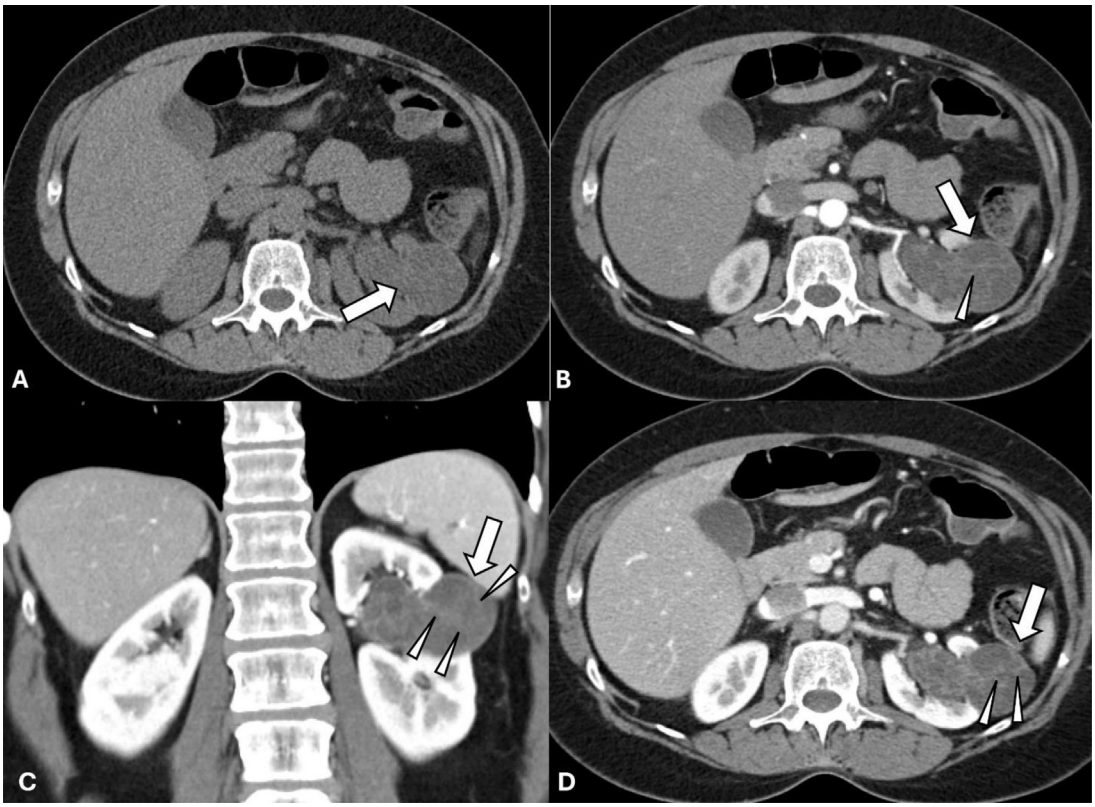

Fig. 7 – 51-year-old found with incidental left cystic mass. Axial unenhanced (A), axial (B) and coronal (C) arterial phase contrast-enhanced, and axial nephrographic phase contrast-enhanced (D) CT demonstrate a circumscribed, mildly lobulated, partially exophytic, multiseptated left interpolar cystic structure (arrows). There is associated mild enhancement of multiple internal septa (arrowheads) without calcifications or discrete mural nodule.

weeks. She had 22.3 kg of intentional weight loss over eight months and noticed a bulge in her left abdomen at the end of this period. CT (Fig. 8) showed a large 23.8 cm left renal cystic mass with thick enhancing septa and solid components, consistent with a Bosniak Type IV cyst. Differential diagnosis included MEST and low grade multilocular cystic renal neoplasm. (Fig. 9)

The patient then underwent laparoscopic converted to open left radical nephrectomy with an unremarkable postoperative course. Histopathological analysis of the left kidney specimen showed a large multiloculated cystic mass with areas of solid yellow septa consistent with MEST. There was no evidence of recurrence or lymphadenopathy on subsequent follow up imaging.

Case 7

A 75-year-old male with history of diabetes and advanced squamous cell carcinoma of the left forefinger underwent preoperative assessment with staging CT (Fig. 10 A, B). A 4.6 cm left renal cystic structure was seen with a 1.3 cm enhancing mural nodule and punctate peripheral calcifications. Follow up MRI (Fig. 10 C, D) was ordered which further characterized the lesion as Bosniak Type IV.

The patient then underwent left robotic radical nephrectomy with a postoperative course that was complicated by colonic adhesions later repaired by robotic colporrhaphy. Histopathology of the surgical specimen showed a $6.0 \times 6.0 \times 3.5$ cm cystic mass with solid component and areas of peripheral focal calcification. The specimen was reviewed at the intradepartmental consensus conference and determined to be a MEST. Subsequent imaging did not demonstrate recurrence of the pathology.

Discussion

MEST represent a distinct entity within the renal pathology spectrum, predominantly affecting perimenopausal women with a mean age of 49. While the lesion primarily occurs in females, studies—including our own—continue to document infrequent cases in older men, highlighting the importance of considering this diagnosis across genders. This discussion includes our observations and correlates them with existing literature, focusing on clinical findings, diagnosis, treatment, differentials, and the role of radiographic consultation.

Our case series (summarized in Table 1) has found that MEST typically presents with acute onset flank or lower back pain, prompting further evaluation with ultrasound or CT. Many cases, both in our series and in the literature, have also been discovered incidentally. Notably, previous case reports

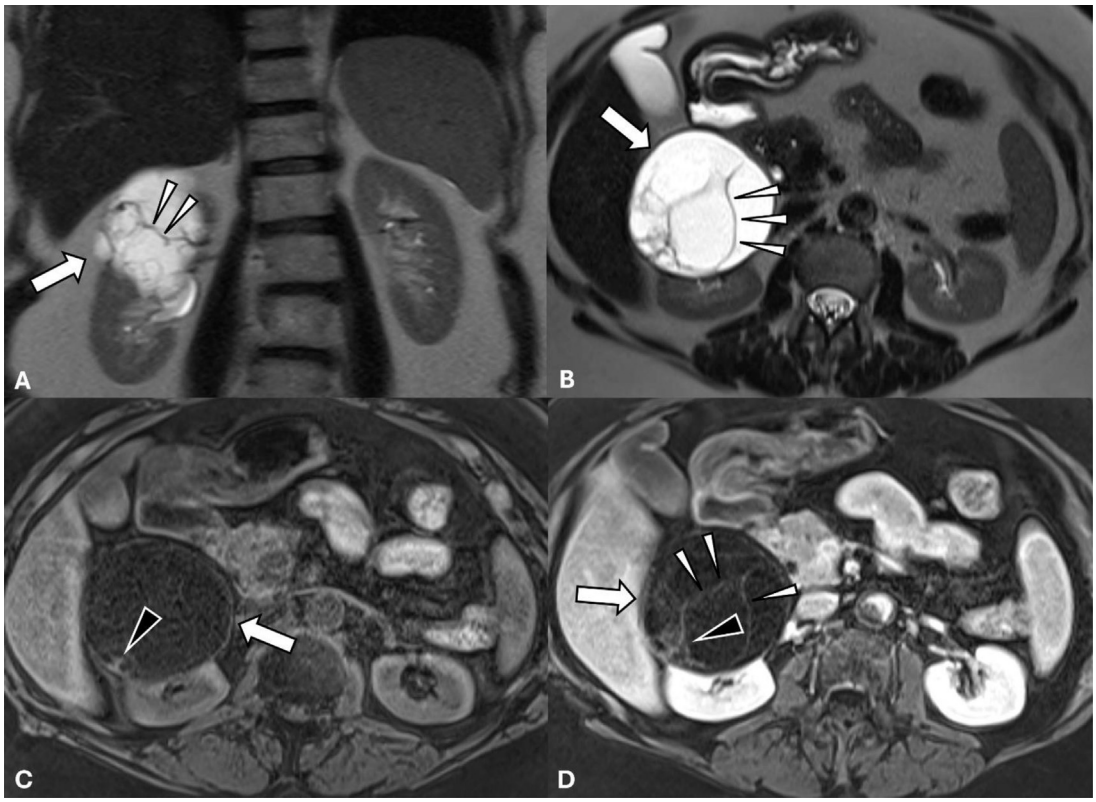

Fig. 8 – Coronal T2 (A), axial T2 (B), axial T1 precontrast (C) and postcontrast (D) MRI abdomen demonstrates a complex, multiseptated, partially exophytic, cystic lesion (arrow) in the interpolar right renal with enhancing septations (white arrowhead) along the right posterior lateral border of the lesion. Early mural nodularity is also noted along the right lateral border (black arrowhead).

Table 1 – Clinical and radiological findings of 7 patients with MEST of the kidney.

Finding	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Gender	F	F	F	F	F	F	M
Age	49 y	52 y	74 y	51 y	59 y	61 y	75 y
Clinical Symptom(s)	Flank pain	Lower back pain	Microscopic hematuria	Incidental	Incidental	Flank pain	Incidental
Exogenous estrogen therapy and/or related medications	N	N	Y	N	Y	N	N
Maximum Size (cm)	2.1	8.9	11.5	5.0	9.0	25.0	6.0
Internal Septations	Y	Y	Y	Y	Y	Y	N
Exophytic	N	Y	Y	Y	Y	N	Y
Bosniak Classification	III	III	IV	IV	III	III	IV
Nodule	N	N	Y	N	Y	N	Y
Enhancement	Y	Y	Y	Y	Y	Y	Y
Mural Calcifications	Y	Y	N	N	N	N	Y

have also identified a history of hormonal therapy, such as androgenic deprivation or estrogen therapy, as having a correlative effect. This hypothesis is physiologically plausible, as the stromal component of MEST consists of spindle cells that resemble ovarian stroma and express estrogen and progesterone receptors [5,11]. We described two MEST cases with previously documented estrogen replacement or selective estrogen receptor modulator therapy. In cases of complex cystic renal lesions, previous history of breast cancer or hysterectomy with bilateral salpingo-oophorectomy warrants deeper investigation into patient medication history for selective estrogen receptor modulators such as tamoxifen in Case 3 or hormone replacement therapy with estradiol as described in Case 5.

Given their rare nature and infrequent occurrence, imaging guidelines for MEST are not well established. A feared malignant mimic of MEST on radiological evaluation is cystic clear cell renal cell carcinoma (ccRCC). The aggressive nature of ccRCC precipitates a need to diagnose and treat potential

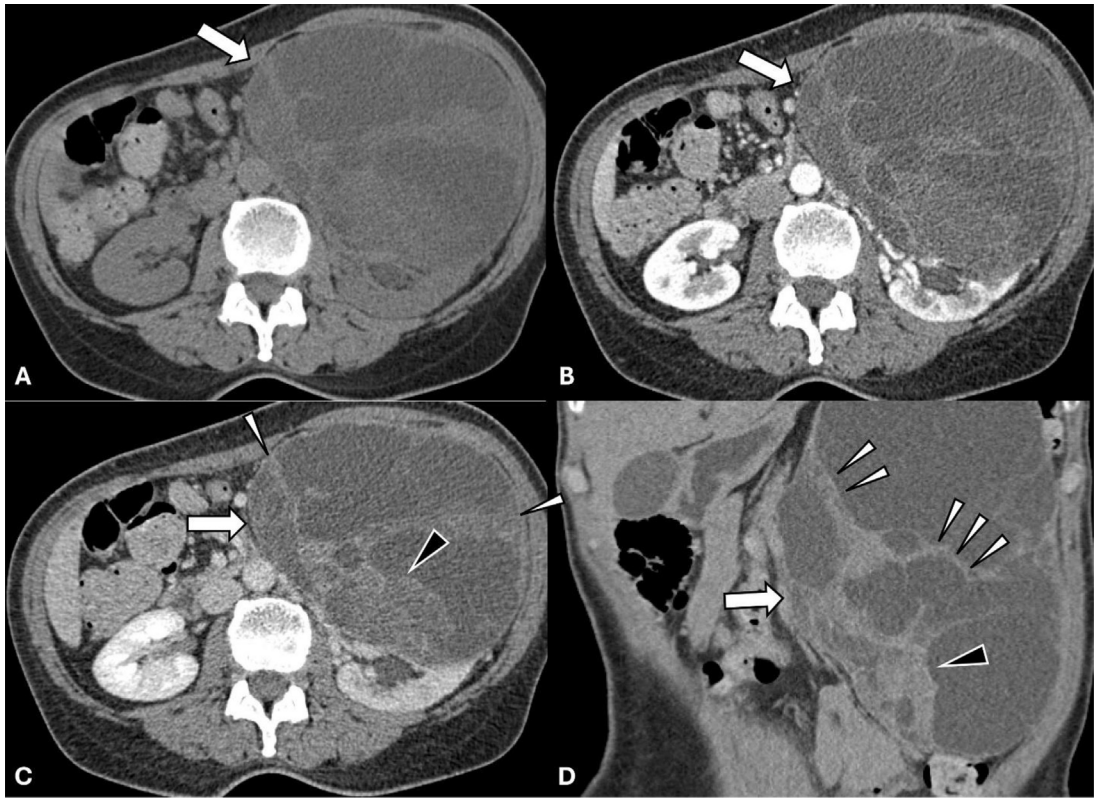

Fig. 9 – 61-year-old with flank pain. Axial unenhanced (A), axial corticomedullary phase contrast-enhanced (B), nephrographic phase contrast-enhanced (C), and coronal (D) excretory phase contrast-enhanced CT demonstrate a large left renal cystic mass (arrows) centered about the anterior interpolar cortex, with multiple thickened septa (white arrowheads) with possible nodular component (black arrowheads).

lesions at a curable stage. This has resulted in resections of indolent cancers and benign renal neoplasms that may not have clear benefit [15]. The Bosniak Classification is the current guideline for characterization of radiological features in unknown cystic renal lesions and risk stratification for malignancy potential. Updates to these guidelines have further clarified differences between classifications and over time have decreased the number of benign and indolent lesions that were previously resected under Bosniak III classification.

In all of our cases, lesions were classified as either Bosniak III or IV on initial radiological imaging, which confer a malignancy risk of approximately 55% and 91% respectively [18]. In the case of Bosniak III cysts, there is some evidence to suggest that active surveillance could be an appropriate alternative to surgery, specifically in cases where lesions are < 4.0 cm [4,19]. Of particular concern are lesions which exhibit rapid interval growth or a significant increase in contrast uptake on interval imaging, as this may represent malignant transformation.

Most imaging evaluations for MEST are performed via CT of the abdomen and pelvis with contrast or MRI with and without contrast. Ultrasound in isolation is typically insufficient, as in Case 1, which necessitated CT for comprehensive evaluation. MEST typically appears as a multiloculated cystic renal mass with a variable ratio of solid to cystic components. Internal septa may demonstrate heterogeneous and delayed contrast material enhancement (Cases 1, 2, 4, 5, 6). Due to variations in the spindle cell components of this tumor, the extent of enhancement can vary significantly, with more intensity in cellularly dense areas and minimal enhancement in fibrotic areas [6,11]. The inherent variability of this tumor renders diagnosis via imaging difficult and unreliable. For this reason, imaging is used alongside clinical features to guide diagnosis.

Additionally, MEST is notorious for mimicking a variety of benign and malignant lesions on imaging. This study identified cystic renal cell carcinoma and abscesses as the top differentials listed by physicians. For instance, distinguishing MEST from cystic renal cell carcinoma proved challenging, as both represented a Bosniak category III or IV lesion. However, cystic RCC is noted to occur more commonly in older men, have more irregularly enhancing septa and enhancing nodular and cystic components. While some case reports in the literature have reported calcifications as an additional distinguishing feature, benign renal cysts frequently exhibit calcifications, thus calcifications are not specific to MEST (Cases 1, 2, 7). MEST can also mimic an abscess, however clinical features such as fever and laboratory testing can usually distinguish this differential diagnosis. Although MEST is a benign neoplasm, our cases demonstrate that it may commonly mimic lesions with malignant potential or cause symptoms such as flank pain and hematuria. For this reason, nephron sparing surgery or radical surgical resection remain the treatment of choice and histopathological assessment is the only method

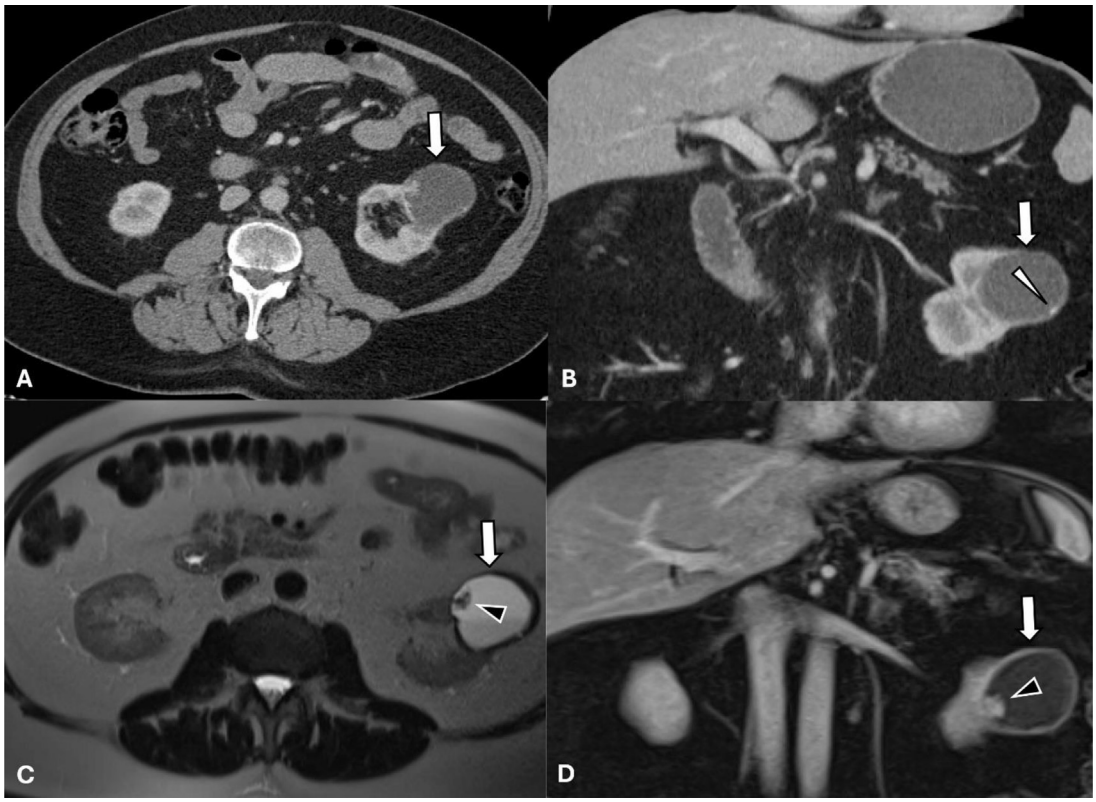

Fig. 10 – 75-year-old found to have a complex left renal mass incidentally. Axial (A) and coronal (B) portal venous phase contrast-enhanced CT demonstrated a left cystic structure with an enhancing mural nodule (arrows) and tiny peripheral calcification (white arrowhead). Axial T2 (C) and coronal T1 postcontrast (D) demonstrate a well-circumscribed, complex exophytic cyst that arises from the lateral interpolar cortex with thick enhancing walls. A 1.3 cm mural nodule (black arrowheads) along the anteromedial wall of the cyst is T2 hypointense and enhancing.

of definitive diagnosis. Although extremely rare, malignant MESTs have been reported in the literature, and this also cannot be excluded without histopathological and immunohistochemical studies [20]. Therefore, surgical excision can be both diagnostic and curative in cases where there is no evidence of metastatic disease [4].

Gross pathology of the resected MEST specimen typically shows solitary, often unilateral lesions (though possible bilateral cases do not preclude diagnosis such as in Case 1), ranging from 2 to 25 cm in size, with a mean size of approximately 9 cm, and variable local involvement of the medulla or pelvis [1,16,17].

Postoperative management is dependent on surgical margins and whether pathological determination of the tumor is benign or malignant. There have been case reports showing local or distant recurrence in the case of malignant MEST, while surgery is curative for benign cases. Management recommendations remain individualized at the discretion of treating physicians given the paucity of evidence in the literature. Malignant lesions may benefit from systemic chemotherapy and surveillance imaging every 6-12 months to monitor for recurrence [20,21]. Guidance is less clear for benign lesions, with some patients in our study undergoing surveillance imaging every 3-12 months and others only following up as needed.

Conclusion

Mixed epithelial and stromal tumors of the kidney are rare benign kidney neoplasms that can present with high variability in both clinical presentation and diagnostic evaluation. This case series highlights the importance of radiological imaging in active surveillance, guiding the diagnosis, and preoperative planning.

Patient consent

Written informed consent for publication of this case was obtained from the patient.

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