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Research Article

Mucinous Tubular and Spindle Cell Carcinoma of the Kidney: A Case Series of Three Patients Including Rare Presentations and Histological Variants

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ABSTRACT
Background: Mucinous Tubular and Spindle Cell Carcinoma (MTSCC) is a rare subtype of renal cell carcinoma (RCC), typically characterized by a biphasic pattern of tubules and spindle cells embedded in a mucinous stroma. It presents diagnostic challenges due to overlapping features with other RCC subtypes. Most cases are detected incidentally. **Objective:** To describe the clinicopathological characteristics and diagnostic challenges of MTSCC through a series of three cases with varying presentations and histological features. **Case Presentation:** Case 1: A 59-year-old male presented with non-specific abdominal pain and chronic constipation. Imaging revealed an exophytic lesion in the left kidney. Partial nephrectomy and histopathology confirmed MTSCC with low-grade features and focal capsular invasion. Case 2: A 47-year-old female presented with intermittent hematuria and flank pain. Imaging detected a well-circumscribed lesion in the lower pole of the left kidney. Radical nephrectomy was performed. Histology showed MTSCC with epithelial predominance and oncocytic changes. Case 3: A 64-year-old asymptomatic postmenopausal female was evaluated for uterine bleeding. Incidental renal mass was found on MRI. Partial nephrectomy revealed classic MTSCC with focal high-grade transformation, characterized by increased mitoses and nuclear atypia. **Results:** All cases demonstrated classic biphasic histomorphology. Immunohistochemistry showed CK7 and PAX8 positivity and CD10 negativity in all three cases. The Ki-67 index ranged from <5% in low-grade tumors to ~20% in areas of high-grade transformation. No metastases were detected, and all patients were placed on surveillance. **Conclusion:** MTSCC is an indolent renal tumor with distinct histological and immunohistochemical features. Although typically low-grade, some tumors may exhibit aggressive behavior, underscoring the importance of accurate histopathological evaluation. Close follow-up is recommended due to the potential for high-grade transformation and recurrence.

INTRODUCTION

Renal cell carcinoma (RCC) encompasses a diverse group of malignancies arising from the renal epithelium and represents approximately 2-3% of all adult cancers. The World Health Organization (WHO) classifies RCC into multiple histological subtypes based on distinct morphological, molecular, and immunohistochemical features. Among these, Mucinous Tubular and Spindle Cell Carcinoma (MTSCC) is a rare, low-grade renal neoplasm that accounts for less than 1% of all RCC cases. Initially characterized in the 2004 WHO classification of tumors of the kidney, MTSCC has since been increasingly recognized due to advancements in diagnostic histopathology and immunohistochemistry.[1]

MTSCC predominantly affects adult females, with a reported female-to-male ratio of approximately 4:1. The median age at diagnosis is around the sixth decade of life, although cases have been reported in a wide age range from adolescence to elderly individuals. Clinically, the majority of MTSCC cases are discovered incidentally during imaging studies performed for unrelated reasons. Symptomatic cases may present with nonspecific signs such

as flank pain, hematuria, or a palpable mass, although these are uncommon.[2]

Radiologically, MTSCC presents as a well-circumscribed, hypovascular mass, often located in the renal cortex. Due to its relatively indolent behavior and nonspecific imaging features, it may be mistaken for other hypovascular renal tumors such as papillary RCC or chromophobe RCC. Hence, definitive diagnosis requires histopathological confirmation. On microscopic examination, MTSCC exhibits a characteristic biphasic morphology comprising elongated, tightly packed tubular structures and interspersed fascicles of bland spindle cells embedded within a mucinous or myxoid stroma. The absence of significant nuclear atypia, mitotic activity, and necrosis are features supporting its low-grade behavior.[3]

Immunohistochemically, tumor cells in MTSCC typically express markers such as cytokeratin 7 (CK7), PAX8, epithelial membrane antigen (EMA), and alpha-methylacyl-CoA racemase (AMACR). They are usually negative for CD10 and CD117, helping to distinguish MTSCC from clear cell RCC and chromophobe RCC respectively. Ki-67, a marker of cellular proliferation, is generally low in classic MTSCC but may be elevated in cases showing high-grade transformation. Recent molecular studies have demonstrated alterations involving the Hippo signaling pathway genes such as NF2, PTPN14, and SAV1, which may have diagnostic and prognostic relevance.[4]

The clinical behavior of MTSCC is generally indolent, with most cases being cured with surgical excision alone. Nephron-sparing surgery is often feasible given the small size and peripheral location of these tumors. However, rare cases have demonstrated aggressive behavior, including local recurrence, high-grade transformation, and distant metastasis. These high-risk cases tend to exhibit features such as increased mitotic activity, sarcomatoid differentiation, necrosis, or vascular invasion.[4] Given the rarity of MTSCC and the limited literature on its long-term outcomes, each case provides valuable insight into the disease's spectrum of presentation and behavior. In this case series, we present three patients diagnosed with MTSCC, each illustrating a distinct clinical and pathological profile: one with classic low-grade morphology, another with epithelial predominance, and the third with focal high-grade transformation. Through this report, we aim to highlight the diagnostic approach, histopathological characteristics, and the importance of long-term follow-up in MTSCC.[5]

The first case involves a 59-year-old male with vague abdominal complaints and incidental detection of a renal mass on imaging. The tumor was confirmed to be MTSCC on histopathology following partial nephrectomy and showed typical biphasic morphology with focal capsular invasion but no high-grade features. The second case discusses a 47-year-old symptomatic female presenting with hematuria, whose imaging revealed a well-defined left renal mass. Radical nephrectomy and subsequent histological examination revealed MTSCC with epithelial predominance and oncocytic change, further confirmed by immunohistochemistry. The third case illustrates the incidental detection of MTSCC in a 64-year-old postmenopausal female being evaluated for abnormal uterine bleeding. While the tumor demonstrated classic MTSCC features, focal areas of high-grade transformation with increased mitoses and nuclear atypia were noted, emphasizing the spectrum of biological behavior that this tumor can exhibit.

In this series, we also underscore the significance of accurate immunohistochemical profiling and careful histopathological evaluation in distinguishing MTSCC from its mimics. The implications of high-grade transformation and the subsequent need for close surveillance are also discussed in light of recent literature. These cases contribute to the growing body of evidence on the clinicopathological diversity of MTSCC and support the role of personalized management strategies in optimizing patient outcomes.

CASE 1: Classic Mucinous Tubular and Spindle Cell Carcinoma (MTSCC) in a 59-Year-Old Male Presenting with Nonspecific Abdominal Symptoms

A 59-year-old male presented to the internal medicine outpatient department with non-specific complaints of dull, intermittent abdominal pain and chronic constipation for the past two months. The abdominal discomfort was described as diffuse, non-colicky, and non-radiating, without any relation to food intake or bowel movements. There was no history of vomiting, fever, gastrointestinal bleeding, urinary frequency, urgency, hematuria, weight

loss, or appetite changes. The patient denied any history of known chronic illness, smoking, or alcohol intake.

Clinical Examination

On general physical examination, the patient was found to be hemodynamically stable:

- Pulse: 74 beats per minute
- Blood Pressure: 122/78 mmHg
- Respiratory Rate: 16 breaths per minute
- Temperature: Afebrile
- SpO_2: 98% on room air

There were no signs of pallor, icterus, edema, or lymphadenopathy. Abdominal examination revealed a soft, non-distended abdomen with no tenderness, palpable mass, or organomegaly. Renal angles were non-tender, and systemic examination of the cardiovascular, respiratory, and neurological systems was within normal limits.

Laboratory Investigations

To evaluate his symptoms, the patient underwent baseline laboratory investigations:

- Complete Blood Count (CBC): Hemoglobin – 13.6 g/dL; WBC and platelet counts – within normal limits
- Renal Function Tests (RFTs): Serum creatinine – 0.92 mg/dL; Blood urea nitrogen – 30 mg/dL
- Liver Function Tests (LFTs): Within normal limits
- Urinalysis: Normal; no hematuria, pyuria, or proteinuria
- Fasting Blood Glucose and Electrolytes: Normal

All values were within physiological limits, indicating no biochemical evidence of renal dysfunction or systemic illness.

Radiological Imaging

Due to the persistent abdominal discomfort and absence of gastrointestinal causes, the patient underwent ultrasound (USG) of the whole abdomen. The USG revealed a heterogeneous nodular lesion located in the upper pole of the left kidney, raising suspicion of a renal mass.

To further characterize the lesion, a CT Urography was performed. The imaging demonstrated:

- Bilaterally functional kidneys
- An exophytic, heterogeneously enhancing mass in the upper pole of the left kidney, measuring approximately 2.5 cm in its largest diameter
- No evidence of renal vein thrombosis, lymphadenopathy, perinephric fat stranding, or contralateral lesions

The radiologic impression was consistent with a renal neoplasm, likely a non-clear cell variant of renal cell carcinoma (RCC) due to its hypovascular appearance.

To evaluate the lesion for metabolic activity and staging, a PET/CT scan was performed. It revealed a heterogeneously enhancing exophytic soft tissue lesion in the upper pole of the left kidney with no evidence of FDG-avid metastatic deposits in the lungs, liver, bones, or lymph nodes, confirming it to be a primary localized renal neoplasm.

Surgical Intervention

Considering the small size, peripheral location, and absence of metastasis, the case was discussed in a multidisciplinary tumor board, and the decision was made to proceed with nephron-sparing surgery. The patient underwent an elective left partial nephrectomy, which was performed without intraoperative complications.

Pathological Examination:

Gross Pathology: The resected specimen consisted of part of the left kidney measuring approximately 5.0 × 4.0 × 3.0 cm. The tumor mass, located at the upper pole, measured 2.5 × 1.5 × 1.0 cm. On cut section, the lesion appeared: Well-circumscribed. Solid and homogeneous. Tan-grey in color. No evidence of hemorrhage, necrosis, or cystic degeneration.

The renal capsule was intact, and surrounding renal parenchyma appeared unremarkable.

Microscopic Examination:

Histological sections revealed a biphasic tumor pattern composed of: Elongated, anastomosing tubular structures lined by low-grade cuboidal epithelial cells with uniform, round nuclei, inconspicuous nucleoli, and scant mitotic activity. Interspersed bland spindle cells embedded within an abundant myxoid (mucinous) stroma. The architectural pattern was classic for Mucinous Tubular and Spindle Cell Carcinoma (MTSCC). Focal invasion into the renal capsule was noted, but no vascular invasion, necrosis, or perinephric fat infiltration was seen

Immunohistochemical Profile

An IHC panel was applied to confirm diagnosis and exclude morphologic mimics such as papillary RCC or sarcomatoid carcinoma: CK7: Positive (diffuse cytoplasmic staining). PAX8: Positive (nuclear staining; confirms renal epithelial origin). CD10 and CD117: Negative (ruling out clear cell RCC and chromophobe RCC, respectively)

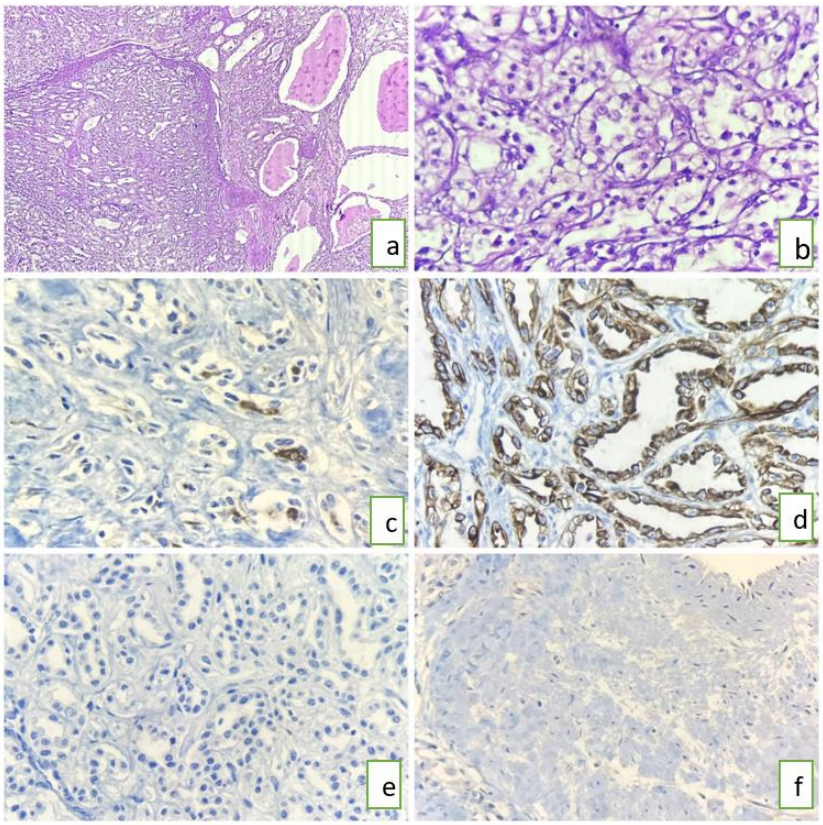

Figure 1: a: low power image showing tubules formation alongwith spindle cell proliferation; b: high power image showing tubules lined by cuboidal cells; c: PAX8: nuclear positivity; d: CK7: cytoplasmic positivity; e & f: negative immunostaining for CD117 & CD10.

CASE 2: Mucinous Tubular and Spindle Cell Carcinoma with Epithelial Predominance in a 47-Year-Old Female Presenting with Hematuria and Flank Pain

A 47-year-old female presented to the urology outpatient clinic with complaints of intermittent gross hematuria and a dull, persistent left flank pain for the past one month. The hematuria was painless, non-clotting, and occurred sporadically without any apparent triggers. The flank pain was described as non-radiating, low-grade, and not associated with positional changes or physical exertion. There was no associated fever, dysuria, increased urinary frequency, urgency, nocturia, or other lower urinary tract symptoms. She denied any weight loss, anorexia, fatigue, or other constitutional signs.

Her past medical and surgical history was non-contributory. She had no known comorbidities such as diabetes, hypertension, or nephrolithiasis. She was a nonsmoker and had no family history of renal malignancy or genetic syndromes associated with kidney tumors.

Clinical Examination

On physical examination, the patient appeared comfortable and afebrile, with the following vitals:

- Blood Pressure: 124/80 mmHg
- Pulse Rate: 76 bpm
- Respiratory Rate: 16 breaths/min
- Temperature: 36.7°C
- SpO_2: 98% on room air

General physical examination was unremarkable, with no signs of pallor, icterus, edema, lymphadenopathy, or cachexia. Abdominal examination showed a soft, non-distended abdomen with no palpable masses or organomegaly. There was no costovertebral angle tenderness. Cardiovascular, respiratory, and neurological examinations were within normal limits.

Initial Investigations

A battery of laboratory investigations was ordered:

- Complete Blood Count (CBC): Hemoglobin 12.8 g/dL, normal WBC and platelet counts
- Serum Creatinine: 0.8 mg/dL
- Blood Urea Nitrogen: 26 mg/dL
- Electrolytes and Liver Function Tests: Within normal ranges
- Urinalysis: Revealed microscopic hematuria, with 25–30 RBCs/HPF; no proteinuria, casts, or pyuria was observed
- Urine cytology: Negative for malignant cells

Imaging Studies

An ultrasonography (USG) of the abdomen and pelvis was performed as the initial imaging modality. It revealed a well-defined hypoechoic lesion located at the lower pole of the left kidney, suggestive of a solid renal mass.

Subsequent CT Urography confirmed the findings and provided further detail:

- A hypodense, exophytic lesion measuring approximately 3.1 cm in greatest dimension
- The mass was solid, well-circumscribed, and confined to the lower pole of the left kidney
- No calcifications, fat density, or central necrosis was observed
- Perinephric fat planes were preserved, with no regional lymphadenopathy, vascular invasion, or venous thrombus

These findings were highly suggestive of a renal neoplasm, most likely a non-clear cell subtype of renal cell carcinoma.

After evaluation by the multidisciplinary tumor board, considering the size and location of the mass and the absence of metastatic features, the patient was planned for curative surgical resection.

Surgical Intervention:

The patient underwent a left radical nephrectomy through a transperitoneal approach. The intraoperative period was uneventful, and the resected specimen was sent for gross and microscopic pathological examination.

Pathological Findings

Gross Examination

The specimen consisted of the entire left kidney with intact perinephric fat. A well-encapsulated, solid tumor was identified in the lower pole, measuring 3.1 × 2.8 × 2.0 cm. On cut section, the mass was firm, with a homogenous grey-white appearance. There was no evidence of hemorrhage, necrosis, or cystic change. The renal pelvis and ureter were uninvolved, and surgical margins were grossly free of tumor

Microscopic Examination

Histology revealed a biphasic tumor comprising: Elongated, tightly packed tubules lined by uniform cuboidal epithelial cells with low nuclear grade, consistent with the epithelial component. Bland spindle cells arranged in fascicles, interspersed within a mucin-rich (myxoid) stroma. Occasional tubular structures exhibited oncocytic cytoplasmic changes

No evidence of necrosis, increased mitosis, vascular invasion, or perinephric fat extension was noted

The tumor was well-circumscribed, with no infiltrative margins

Immunohistochemical (IHC) Analysis:

To confirm the histological diagnosis and exclude differential diagnoses such as papillary RCC or metanephric adenoma, IHC staining was performed:

CK7: Strong diffuse cytoplasmic positivity

AMACR (Alpha-methylacyl-CoA racemase): Positive

PAX8: Strong nuclear positivity, confirming renal epithelial origin

CD10 and CD117: Negative, ruling out clear cell RCC and chromophobe RCC, respectively

Ki-67 proliferation index: Low (<5%), supporting the low-grade nature of the tumor

CASE 3: Incidental Detection of Mucinous Tubular and Spindle Cell Carcinoma with Focal High-Grade Transformation in a Postmenopausal Female

A 64-year-old postmenopausal female was referred to the gynecology outpatient department for evaluation of abnormal uterine bleeding, which had been intermittent for the past few weeks. She had attained menopause over a decade earlier and had no prior history of gynecological disorders or hormone replacement therapy. She did not report any associated abdominal pain, urinary complaints, hematuria, fever, anorexia, or weight loss. There was no history of flank pain, palpable mass, or constitutional symptoms.

Her past medical history was non-contributory. She was non-diabetic, normotensive, and had no prior renal or gynecological surgeries. There was no family history of malignancies. She did not smoke or consume alcohol.

Clinical Examination and Initial Investigations

On general examination, the patient was afebrile, hemodynamically stable, and in good overall health. Abdominal examination was soft and non-tender, with no organomegaly or

palpable mass. Pelvic examination was unremarkable except for minimal uterine bleeding.

Routine hematological and biochemical investigations were performed as part of the preoperative gynecological workup:

- Complete blood count: Within normal range (Hb 13.2 g/dL, WBC and platelet counts normal)
- Renal function tests: Serum creatinine 0.86 mg/dL, BUN 29 mg/dL
- Electrolytes and liver enzymes: Within normal limits
- Urine routine: Normal; no hematuria or pyuria

Imaging and Incidental Renal Mass Detection:

As part of the evaluation of postmenopausal bleeding, the patient underwent a contrast-enhanced MRI of the abdomen and pelvis, primarily to assess uterine and adnexal structures. Incidentally, a solitary renal mass was identified in the mid-zone of the right kidney. Detailed MRI findings included:

- A spherical, well-circumscribed lesion measuring 3.5 cm in diameter
- The lesion was hypointense on T2-weighted imaging and demonstrated minimal post-contrast enhancement
- There were no signs of perinephric fat infiltration, lymphadenopathy, or involvement of renal vessels

The imaging characteristics were suggestive of a hypovascular renal tumor, prompting urological referral for further evaluation. Differential diagnoses considered included papillary RCC, chromophobe RCC, and less commonly, MTSCC or metanephric adenoma.

In view of the lesion's small size, localized nature, and absence of metastasis, the patient was planned for nephron-sparing surgery.

Surgical Management

A laparoscopic partial nephrectomy was performed uneventfully. The tumor was successfully excised with adequate margins, and the specimen was sent for detailed gross and histopathological evaluation.

Pathological Examination

Gross Findings: The resected tumor was well-encapsulated, measuring 3.5 × 3.0 × 2.5 cm. The cut surface was solid, homogenous, and grey-white in color, without any areas of necrosis, hemorrhage, or cystic change The tumor was well demarcated from the surrounding renal parenchyma, with no gross evidence of capsular breach or renal sinus involvement

Microscopic Findings

Histopathological analysis revealed a biphasic neoplasm characteristic of Mucinous Tubular and Spindle Cell Carcinoma (MTSCC)

The tumor showed: Tightly packed, elongated tubules lined by low-grade cuboidal epithelial cells. Interspersed fascicles of bland spindle cells embedded in abundant myxoid (mucin-rich) stroma

Importantly, focal areas exhibited features of high-grade transformation, including: Nuclear pleomorphism and hyperchromasia. Increased mitotic figures (>5 per 10 high-power fields). Focal infiltrative growth pattern extending toward the renal capsule

There was no lymphovascular invasion, no perinephric extension, and surgical margins were free of tumor

Immunohistochemistry (IHC)

To confirm the renal origin and subtype, and to differentiate it from histological mimics, IHC panel was employed:

Positive markers: CK7: Diffuse and strong cytoplasmic staining. CK19: Focal positivity. PAX8: Strong nuclear positivity confirming renal epithelial origin. Vimentin: Positive in both epithelial and spindle cell components

Negative markers: CD10: Negative (rules out clear cell RCC). S100: Negative (rules out neural/melanocytic tumors)

Ki-67 labeling index: Elevated (~20%) in high-grade areas, indicative of increased proliferative activity and supporting the presence of high-grade transformation.

DISCUSSION

Mucinous Tubular and Spindle Cell Carcinoma (MTSCC) represents a unique and rare subtype of renal cell carcinoma (RCC), recognized for its low-grade morphology and distinctive histological features. First described in the 2004 WHO classification of renal tumors, MTSCC was initially termed a low-grade variant of collecting duct carcinoma and was categorized under RCC, unclassified. With increasing case recognition and evolving diagnostic tools, it is now distinctly classified, supported by characteristic histological and immunohistochemical profiles.[6]

The diagnosis of MTSCC is often incidental, as the majority of patients remain asymptomatic at the time of detection. Radiological investigations performed for unrelated complaints commonly reveal these tumors, as highlighted in the present series. When symptoms do occur, they tend to be nonspecific, including flank pain, hematuria, or abdominal discomfort, which may lead to further evaluation with imaging modalities.[7]

MTSCC predominantly arises from the renal cortex but may also extend into the medulla. On imaging, these tumors present as well-demarcated, spherical to ovoid exophytic masses with expansile growth patterns. On contrast-enhanced CT, MTSCC typically appears hypovascular, necessitating differentiation from papillary RCC and chromophobe RCC—two renal neoplasms that share overlapping radiological features.[8]

Macroscopically, MTSCCs are usually solid, well-circumscribed tumors with a grey-white, tan, or yellow cut surface. Microscopically, they exhibit a biphasic architectural pattern consisting of tightly packed, elongated, and anastomosing tubules lined by bland, low-grade cuboidal epithelial cells intermixed with fascicles of spindle-shaped cells within a myxoid stroma. Depending on the dominant morphological component, tumors may be classified as spindle cell predominant, epithelial cell predominant, or mucin-poor variants. Occasional oncocytic changes or clear cytoplasm can also be observed.[3]

Although MTSCC is primarily considered an indolent neoplasm, certain cases exhibit aggressive features. Histological signs of high-grade transformation—such as nuclear pleomorphism, increased mitotic activity, necrosis, vascular invasion, and infiltrative growth patterns—are associated with a worse prognosis. Such tumors have been linked to regional lymph node involvement and distant metastases, including pulmonary and skeletal sites. High-grade transformation was observed in one of the cases in this series, underlining the heterogeneity in MTSCC behavior.[5]

Immunohistochemically, MTSCC demonstrates positivity for several markers including cytokeratin 7 (CK7), PAX8, cytokeratins 8/18, CK19, epithelial membrane antigen (EMA), alpha-methylacyl-CoA racemase (AMACR), and vimentin. These features support its epithelial and renal tubular origin. Tumors are typically negative for CD10 and CD15, aiding in distinction from clear cell RCC and papillary RCC. In high-grade areas, increased expression of Ki-67 and nuclear accumulation of p53 may be seen, reflecting heightened proliferative activity.[7]

Although initially thought to arise from the loop of Henle or the collecting duct system due to its architecture, immunophenotypic studies suggest a proximal nephron origin. The expression of CK7 and AMACR, markers associated with proximal tubules, reinforces this hypothesis. Molecular studies have shown that MTSCC harbors recurrent chromosomal losses involving chromosomes 1, 4, 6, 8, 9, 11, 13, 14, 15, 18, 22, and X. Whole exome sequencing has revealed biallelic inactivation of tumor suppressor genes involved in the Hippo signaling pathway, notably PTPN14, NF2, and SAV1. These findings offer insight into the tumorigenesis of MTSCC and may have implications for future diagnostic and therapeutic advancements.[8]

Management of MTSCC primarily involves surgical resection. Nephron-sparing surgery is often adequate for low-grade, localized tumors. Radical nephrectomy may be performed in cases with larger or more centrally located tumors. There is currently no standardized systemic therapy for metastatic MTSCC. In the absence of specific guidelines, therapies used for clear cell RCC—such as VEGF inhibitors or immune checkpoint inhibitors—have been used anecdotally in advanced MTSCC with variable results. Therefore, early diagnosis and complete surgical excision remain the mainstay of treatment.[10]

Importantly, although classic MTSCC is associated with a favorable prognosis, isolated cases of low-grade tumors with late metastases have been reported. This unpredictability mandates long-term follow-up even in patients with completely resected, histologically low-grade tumors. Surveillance should include periodic imaging and clinical monitoring.[11]

CONCLUSION

Mucinous Tubular and Spindle Cell Carcinoma (MTSCC) is a rare and distinctive subtype of renal epithelial malignancy that typically presents with low-grade morphological features and indolent clinical behavior. Despite its relatively favorable prognosis, MTSCC exhibits a histological spectrum that may include high-grade transformation in rare cases, underscoring the need for careful diagnostic and prognostic assessment. Surgical excision—either partial or radical nephrectomy depending on tumor size and location—remains the

cornerstone of treatment. Immunohistochemical evaluation plays a critical role in establishing the diagnosis and ruling out mimickers such as papillary RCC and chromophobe RCC.

While most cases do not require systemic therapy, the occasional occurrence of aggressive histological features such as increased mitotic activity, nuclear atypia, or infiltrative growth patterns demands a cautious approach. Furthermore, emerging molecular insights, including alterations in the Hippo signaling pathway, offer potential avenues for future targeted therapies.

In view of these factors, long-term surveillance is recommended even in cases with classic low-grade morphology to monitor for rare instances of late recurrence or metastasis. Multidisciplinary collaboration and individualized patient management are essential for optimizing outcomes. Continued documentation and analysis of MTSCC cases are vital to expand our understanding of its clinical course, molecular underpinnings, and therapeutic responsiveness.

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