Mucinous Tubular and Spindle Cell Carcinoma
A Review of Histopathology and Clinical and Prognostic Implications

Shrinidhi Nathany, MBBS; Vidya Monappa, MBBS, MD

• Mucinous tubular and spindle cell carcinomas are rare kidney tumors with generally indolent behavior. As the name suggests, classic histomorphology reveals bland spindle cells, tubules, and mucinous stroma. Uncommon histologic features include mucin-poor stroma, high nuclear grade, cellular pleomorphism, and presence of necrosis. Rare cases can show aggressive growth and distant metastasis. Mucinous tubular and spindle cell carcinoma has characteristic chromosomal abnormalities and the molecular signature remains the same, irrespective of the varied histomorphology.

Mucinous tubular and spindle cell carcinoma (MTSCC) of the kidney is a rare epithelial neoplasm of low malignant potential with characteristic histologic features. The earliest cases were reported by Ordonez and Mackay and MacLennan et al as “RCC [renal cell carcinoma] with unusual differentiation, originating in loop of Henle” and “low grade collecting duct carcinoma,” respectively. As a distinct entity, MTSCC was first reported in a series of 4 cases of low-grade renal tumors with myxoid appearance and distal nephron differentiation by Parwani et al. Mucinous tubular and spindle cell carcinoma was first included in the 2004 edition of the World Health Organization classification of RCCs, and in the recent update has gained importance owing to prognostic and therapeutic differences. Since then, fewer than 100 cases have been reported in the literature, with varied clinicopathologic characteristics and molecular features. As the name suggests, MTSCC is morphologically composed of 3 elements: spindle cells, tubules, and extracellular myxoid or mucinous stroma. The clinical course and prognosis are not well understood. In this short review, we highlight the clinical, pathologic, immunohistochemical, and molecular aspects of the tumor, along with the differential diagnoses, clinical behavior, and prognosis.

CLINICAL CHARACTERISTICS

According to the World Health Organization 2016 “blue book,” this tumor accounts for less than 1% of all renal tumors. It is a tumor primarily of adulthood, with a mean age of 58 years (range, 13–81 years). Mucinous tubular and spindle cell carcinoma shows a female preponderance, with a female to male ratio of 3:1. In the original study of Parwani et al, all 4 reported cases were female, with a mean age of 50 years. Thereafter, many reports and series revealed a similar age and sex incidence with respect to this lesion.

The majority of the tumors are incidentally detected on abdominal imaging for other unrelated reasons. However, some may present with hematuria, flank pain, and a palpable abdominal mass. Hes et al reported an association with renal calculi, and Nouh et al reported its occurrence in patients with end-stage renal disease on dialysis for more than 10 years.

The tumor is generally found in the renal cortex, and very rarely may arise in the renal medulla also.

On imaging, MTSCC displays an appearance that is different from that of clear cell RCC but similar to that of papillary RCC. On computed tomography imaging, it typically presents as a well-demarcated, exophytic, spherical or ovoid renal mass and shows an expansile growth pattern. Tumors less than 5 cm usually demonstrate a homogenous pattern of enhancement, whereas those larger than 5 cm are heterogeneous (Figure 1). On contrast-enhanced ultrasonography and contrast-enhanced computed tomography, MTSCC shows a hypovascular pattern and needs to be differentiated from other hypovascular renal tumors like papillary RCC and chromophobe RCC.

GROSS PATHOLOGY

In a recent review of uncommon RCCs, Srigley and Delahunt described the clinicopathologic features of MTSCC and reported that these tumors are macroscopically well circumscribed and solid masses with a homogenous tan, gray-pink, or pale yellow cut surface. Tumor size ranges from less than 1 cm to more than 18 cm in diameter, with most tumors being 2 to 4 cm. Areas of hemorrhage and necrosis are unusual (Figure 2).

HISTOLOGY

Histologically, the tumor is described by a mixture of tubular and spindle cell components, separated by variable amounts of mucinous stroma (Figures 3 through 5). The tubules are round, ovoid, or elongated and anastomosing
with a collapsed central lumen. They are often tightly packed and arranged in parallel and sometimes merge into cordlike structures or even form a solid growth pattern. The tubules may show focally clear cells, oncocytic change, or vacuolations in the cytoplasm. Mucinous tubular and spindle cell carcinoma is a low-grade malignancy, with round nuclei, evenly dispersed chromatin, and occasional nucleoli corresponding to World Health Organization/International Society of Urological Pathology grade 2; however, rare lesions with high-grade atypical nuclei and sarcomatoid change have been described. Transitions between the elongated tubules and the spindle cells are commonly seen, and in some tumors, the spindle cell areas can be the principal component, resembling a mesenchymal neoplasm such as leiomyoma or myofibroblastoma. The stroma shows extracellular mucin, which may be basophilic or occasionally eosinophilic, with a bubbly appearance. The study by Fine et al expanded the histologic spectrum of MTSCC into 2 variants: classic and mucin poor. This categorization was based on a percentage of extracellular mucin and the relative percentage of tubules and spindle cells in the tumor after adequate sampling. They found that 10 of the 17 cases were classic MTSCC and the remaining 7 were the mucin-poor variants with little or no extracellular mucin in the stroma. Other microscopic findings reported in the literature include aggregates of foamy histiocytes, papillations (epithelial tufts that project into the tubular lumina and lack a fibrovascular core), microscopic tumor necrosis, cuffed lymphoplasmacytic infiltrate surrounding tumor cell nests, psammomatous calcifications, and heterotopic bone formation. These findings were described by Fine et al who reported a higher occurrence of these findings in the mucin-poor tumors. Mitoses are usually rare in these tumors, as they are usually low-grade malignancies with a favorable outcome; some tumors with sarcomatoid change show increased and atypical mitoses, marked cytologic atypia, and tumor necrosis.

ANCILLARY TESTING

Immunohistochemistry

The neoplastic cells of both tubules and spindle cells are positive for paired box transcription factor 2 (PAX2) and PAX8, low-molecular-weight cytokeratin (CK)—that is, CK8/18, CK19 and CK7 (Figure 6)—epithelial membrane antigen, α-methylacyl coenzyme A racemase (AMACR), and E-cadherin; 34βE12 and other high-molecular-weight keratins and vimentin show variable expression. CD10, CD15, and RCC marker, which is usually positive in the clear cell variant of RCC, are often negative; however, rare cases with positive expression have been reported. Other markers like carbonic anhydrase IX (CAIX), Ulex europaeus agglutinin 1, p63, CK20, GATA3, and smooth muscle actin are negative. Some cases reported recently showed neuroendocrine differentiation in the tumor cells staining positive for chromogranin A, synaptophysin, and neuron-specific enolase. Increased Ki67 labeling index and high nuclear p53 accumulation were observed in high-grade tumors.
Molecular Genetics and Histogenesis

Mucinous tubular and spindle cell carcinoma was originally described as a tumor arising from cells of the loop of Henle or the collecting duct epithelium. But its origin was later suggested as a tumor arising from cells of the metanephric mesenchyme, with expression of CK7 and AMACR, and its close resemblance to papillary RCC. In some settings, it becomes impossible to distinguish between the two on the basis of routine microscopy, immunohistochemistry, and ultrastructural studies. This necessitates molecular testing for a confident distinction.

Multiple numerical aberrations involving chromosomes 1, 4, 6, 8, 9, 11, 13, 14, 15, 18, 22, and X have been observed in comparative genomic hybridization, cytogenetics, and fluorescence in situ hybridization studies on MTSCC. In a large series of comparative genomic hybridization studies on MTSCC, Peckova et al. reported that the tumors with classic morphology showed loss of chromosomes 1, 4, 6, 8, 9, 13, 14, 15, and 22, whereas the tumors with overlapping features with papillary RCC showed variable losses and gains, including a gain of chromosome 7 and 17. However, later fluorescence in situ hybridization–based studies showed that MTSCC had no gains of 7, 17, and Y and that these aberrations were characteristic for papillary RCC.

Whole-exome and transcriptome sequencing of MTSCC revealed biallelic loss of Hippo signaling pathway suppressor genes, namely PTPN14, NF2, and SAV1. This finding that Hippo pathway dysregulation is an essential causative event in the pathogenesis of MTSCC may have diagnostic and therapeutic ramifications.

Banyai et al. in their recent study on the embryonal origin of MTSCC, proposed that the tumor develops from embryonal rest–like precursor lesions of impaired differentiation. The altered time of mesenchyme to epithelium transition affecting different cell lineages could be the reason for the morphologic variations seen in MTSCC. They were of the opinion that unless genetically proven, mucinous tubular and spindle cell tumor is a better term to describe this tumor.

Differential Diagnoses of Mucinous Tubular and Spindle Cell Carcinoma (MTSCC) With Similarities and Distinguishing Features

<table>
<thead>
<tr>
<th>Entities</th>
<th>Morphology</th>
<th>Distinguishing Morphologic Features</th>
<th>IHC</th>
<th>Molecular Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRCC</td>
<td>Predominantly solid or tubular growth pattern with elongated tubules in type 1 papillary RCC</td>
<td>Predominantly tubulopapillary pattern</td>
<td>CD10 positive in PRCC, negative in MTSCC</td>
<td>Gain of 7, 17, and Y</td>
</tr>
<tr>
<td>Sarcomatoid RCC</td>
<td>MTSCC with a dominant spindle cell component</td>
<td>Spindle cells are neoplastic and bizarre and in sheets</td>
<td>Not useful</td>
<td>Not specific</td>
</tr>
<tr>
<td>Mesenchymal tumors like leiomyoma, AML, IMT, and JCT</td>
<td>Bland spindle cells in fascicles and whorls</td>
<td>Leiomysarcoma: no tubules, no mucinous stroma</td>
<td>Leiomyoma: SMA&lt;sup&gt;+&lt;/sup&gt;, AML: HMB45&lt;sup&gt;+&lt;/sup&gt;, IMT: ALK&lt;sup&gt;+&lt;/sup&gt;, JCT: CD34, renin&lt;sup&gt;+&lt;/sup&gt;</td>
<td>IMT: t(2;5), JCT: loss of chromosomes 9, 11</td>
</tr>
<tr>
<td>Metanephric adenoma</td>
<td>Closely packed narrow tubules</td>
<td>Basophilic cytoplasm, psammoma bodies, absent myxoid stroma</td>
<td>WT1, CD57&lt;sup&gt;+&lt;/sup&gt;</td>
<td>V600E BRAF</td>
</tr>
</tbody>
</table>

Abbreviations: ALK, anaplastic lymphoma kinase; AML, angiomyolipoma; IHC, immunohistochemistry; IMT, inflammatory myofibroblastic tumor; JCT, juxtaglomerular cell tumor; PRCC, papillary RCC; RCC, renal cell carcinoma; SMA, smooth muscle actin.

<sup>a</sup> Data derived from Zhao et al., Ferlicot et al., Peckova et al., Wang et al., and Kuroda et al.

**Mucinous Tubular and Spindle Cell Carcinoma**

In its classic form, MTSCC does not pose a diagnostic problem owing to its distinct morphology. The Table depicts the differential diagnoses based on component variation with distinguishing features and similarities.

**THERAPY AND PROGNOSIS**

Mucinous tubular and spindle cell carcinoma with classic morphology has excellent prognosis subsequent to complete and adequate excision. These tumors are usually low grade and hence are responsive to partial or radical nephrectomy. Some cases reported in the literature have shown recurrence, regional lymph node metastases, and distant metastases. These occur in lesions with high nuclear grade, sarcomatoid transformation, and other atypical histomorphologic features. However, few cases of low-grade tumors with classic morphology have shown metastases in lymph nodes and liver. Hence, a close follow-up is warranted even after complete excision, despite the innocent clinical course of the tumor.

Low-grade, classic-morphology tumors are amenable to resection and do not require systemic chemoradiation. With regard to metastatic tumors, there are no consensus guidelines published to date that warrant systemic treatment.

**CONCLUSIONS**

Mucinous tubular and spindle cell carcinoma is a low-grade malignant renal tumor with characteristic histologic, immunohistochemical, and molecular features, and hence is considered a distinct entity. Most reported cases have been diagnosed as low-grade malignancies and have had a favorable outcome after surgical removal. However, a small subset of cases has been reported with an aggressive clinical phenotype and poor outcome. A close follow-up of these
patients is therefore essential to look for recurrence and/or metastasis.

We thank Tanvi Shetty, MD, assistant professor, Melaka Manipal Medical College, Manipal, and Shubham Varshney, MBBS, junior resident, KMC, Manipal, for the help rendered in collecting case details and images.

References
