Renal mucinous and tubular spindle cell carcinoma: a clinicopathological study of 4 cases

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The clinical and histological findings of four cases of renal mucinous tubular and spindle cell carcinoma (MTSCC) are reported. Two cases were incidentally discovered during the radiological study of other diseases, and the other two presented with haematuria. Radical nephrectomy was done in the four cases. All the tumours showed the typical histology and immunohistochemistry described in this newly recognised entity. The patients remain free of disease after 3, 8, 10 and 48 months of follow up. The literature related to the diagnosis of this tumour is thoroughly reviewed. Also, the proposed histopathogenetic theories for this tumour are also briefly commented on.

The new 2004 WHO classification system of renal tumours is based on morphologic criteria and supported by common genetic findings.[12] Among other rare entities, it includes a variant of renal carcinoma termed mucinous tubular and spindle cell carcinoma (MTSCC). This tumour type had been previously diagnosed as papillary renal carcinoma, metanephric adenoma, unclassified or sarcomatoid carcinoma,[5,8,11,13] and seems to portend a favourable clinical outcome. We report the clinicopathological findings of four additional cases of this rare newly recognised tumour, highlighting its varied histological patterns and differential diagnosis. The cases were collected retrospectively from consultation of our archive in the last 3 years.

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Cases

Case 1 was a 66-year-old woman who presented with painless hematuria. Imaging studies (ultrasound, CT) revealed a left organ-confined renal tumour (Figure 1A). Metastases were not detected in the preoperative work up. A radical left nephrectomy was performed. Grossly, the resected kidney contained an intrarenal solid, well-demarcated, pale and homogenous yellowish to tan tumour, measuring 4×4×5.5 cm in maximum diameter. The tumour compressed, but did not invade, the renal pelvis. There was no evidence of renal vein invasion, and the renal capsule was intact. The patient was asymptomatic and free of disease 48 months after the diagnosis.

Case 2 was a 69-year-old woman with a left renal tumour confined to the inferior pole that was incidentally discovered in the process of evaluating the extension of an in situ low grade mammary papillary solid carcinoma. The patient underwent a right mastectomy and, two months later, a radical left nephrectomy. Grossly, the kidney showed a well-circumscribed tumor measuring 10.5×8×6 cm, located in the lower pole. The cut surface was solid with a greyish to yellowish appearance (Figure 2A). There was no evidence of renal vein invasion or infiltration of the renal capsule. The patient was asymptomatic and free of disease 8 months after the diagnosis.

Case 3 was a 74 year-old woman with a left renal tumour that was accidentally discovered during the clinical work-up of a hiatal hernia (Figure 1B). A total nephrectomy was performed. The tumor was well delimited, measured 3.5×3.2×3 cm, and was confined to the kidney. Renal sinus and perinephric adipose tissues were not invaded (Figure 2B). The patient re-

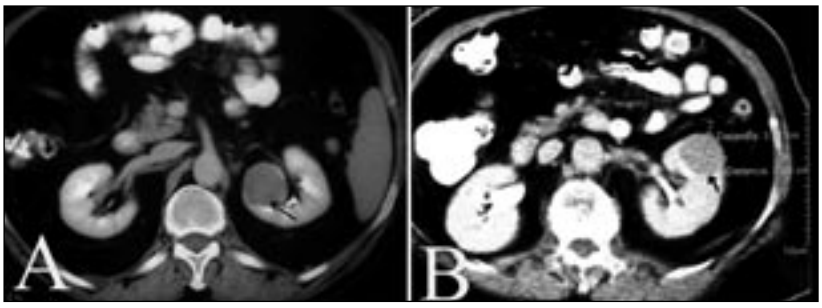

Figure 1. Magnetic resonance showing two tumor masses in the left kidneys of case 1 (A) and case 3 (B).

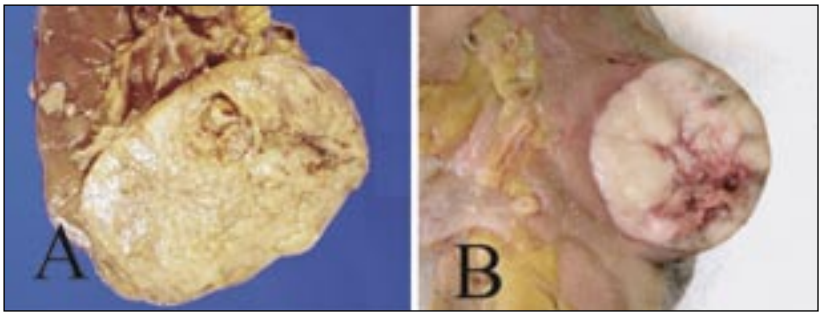

Figure 2. Macroscopic view of two intrarenal tumour masses with a solid yellowish cut surface. Renal vein invasion and infiltration of the renal capsule were not evidenced. Case 2 (A) and Case 3 (B).

mained free of disease 10 months after the diagnosis.

Case 4 was a 49-year-old male who consulted a urologist because of intermittent episodes of hematuria. A 4-cm tumor was discovered in the periphery of the right kidney and a total nephrectomy was subsequently performed. The tumor was of a whitish cut surface and well delimited. Perinephric tissues and the renal sinus were not affected. The patient was asymptomatic in the last follow-up visit, 3 months after surgery.

Histological findings

Histological examination showed similar features in the four cases (Figure 3). They were well-circumscribed masses surrounded by a thin rim of compressed tissue. Solid and tubular areas lying in a focally mucinous basophilic matrix were identified. Tubules were lined by cuboidal cells with eosinophilic cytoplasm, and displayed centrally located round nuclei. Some of the tumor cells had a vacuolated cytoplasm. Intraluminal mucin deposits were observed in many tubules. Solid areas were composed of monotonous sheets of elongated spindle uniform cells with eosinophilic cytoplasm. Tumor cells were focally separated by abundant myxoid stroma containing nests of foamy histiocytes. Atypia was not significant. Vascular and sinus invasion was not observed. Lymph node metastases were not seen.

By immunohistochemistry, tumor cells were diffuse and intensely positive with epithelial membrane antigen (EMA), vimentin and cytokeratins AE1/3 and 34βE12. Focal immunostaining with cytokeratins 7 and 19 were detected. Conversely, cytokeratins 8/18 and 20, villin, CD10, Ki67, p53, chromogranin, synaptophisin, CD57, and high molecular weight cytokeratin (34βE12), were all negative.

Discussion

Mucinous tubular and spindle cell carcinomas are low-grade renal epithelial neoplasms first recognized as a specific entity in the 2004 WHO classification of renal tumours.[4] This entity is defined as a "low-grade polymorphic renal epithelial neoplasm with mucinous tubular and spindle cell features".[10] Prior to this recognition, pathologists used to classify these tumours either as variants of solid papillary renal cell carcinomas with compressed and elongated papillae, as metanephric adenomas, or as unclassified or sarcomatoid carcinomas.[4,5] A limited number of recent studies have described this rare morphologic entity; however, its origin and dif-

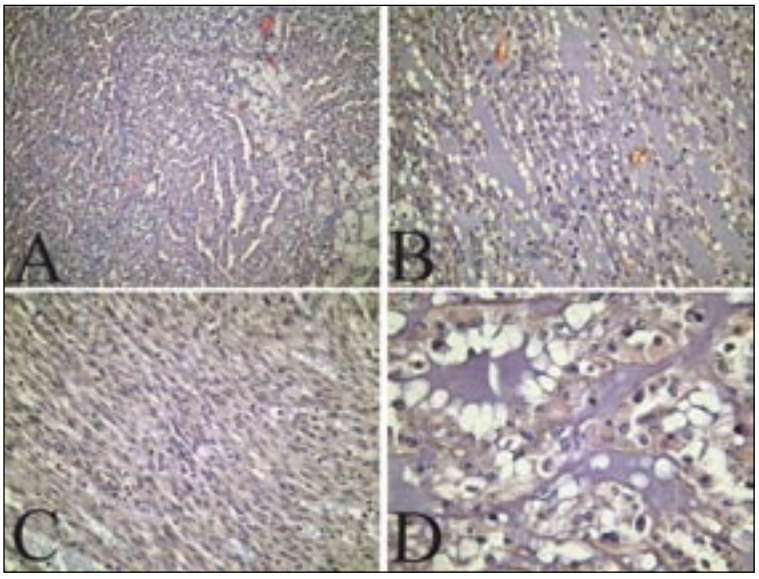

Figure 3. Tumor microscopic view showing mucinous deposition, foamy histiocytes (A), tubular arrangement, and bland cytology (B), high power view of spindle cell (C) and tubular areas (D).

ferentiation remains unclear so far.[13] To date, only 46 cases of MTSCC have been reported.[11] In our experience, this tumor accounts for less than 0.8% of renal neoplasms.

The clinical features of this entity include female predominance, indolent clinical course, and a frequent renal medullary location.[5] Its prognosis is generally favourable, but some cases may show local recurrence or metastasis.[4,9] Grossly, MTSCCs are sharply circumscribed tumors, gray-white, tan, or yellow in colour, and sometimes have minimal foci of hemorrhage or necrosis. Tumor diameter oscillates from 2.2 to 12 cm. Under the microscope, they consist of tightly packed, small, elongated tubules separated by abundant basophilic extracellular mucin. Sparse aggregates of spindled cells may be present. Tubules are lined by uniform low cuboidal cells with scant cytoplasm, and round nuclei of low nuclear grade with absent or inconspicuous nucleoli. Mitotic figures are rare. Generally, these tumours are at a low pathologic stage at the time of excision, and they behave in an indolent fashion.[10] Quite typically, the myxomatous stroma exhibits a positive reaction for Alcian blue and colloidal iron staining.[9]

As reflected by reports in the literature,[3,11,12] tumour cells have a complex and variable immunophenotype. Accumulated evidence suggests these tumours originate either from the collecting duct epithelium or from cells of the loop of Henle. Comparative genomic hybridization studies suggest they arise from the collecting duct epithelium.[10] Immunohistochemistry favours a distal tubule origin (positive for EMA, cytokeratin AE1/3, cytokeratin 7, cytokeratin 19, E-cadherin, alpha-methylacyl-CoA racemase [AMACR]; and negative for CD10).[11] Some MTSCC tumours show a positive reaction for neuron specific enolase (NSE), chromogranin A and/or synaptophysin, results that postulate that MTSCC may be one of the renal neoplasms that frequently exhibit neuroendocrine differentiation.[7,13] Short microvilli and junctional complexes are present on electronic microscopy.[9] Recently, multiple losses of chromosomes 1, 4, 6, 8, 9, 11, 13, 14, 15, 18 and 22 have been demonstrated in some cases by using comparative genomic hybridization,[2,4,9] but the significance of these losses remains obscure to date.

MTSCC are polymorphic neoplasms with a wide range of morphologic variability. Several morphologic variants may cause diagnostic difficulties: some cases may show a predominance of any one of its principal components, as spindle-cell predominant mimicking sarcomatoid carcinomas, or tubular-predominant mimicking solid variant of papillary renal cell carcinoma. Other features include tumours with poor mucin content, areas with extracellular hyaline matrix and blue-tinged mucin within tubules, and solid areas with epithelioid cells. Unusual histologic features include heterotopic bone and calcification, focal moderate atypia (enlarged nuclei/prominent nucleoli), necrosis, oncocytic cells, multinodular growth with lymphocytic

cuffing, and numerous small vacuoles.[3,6]

Histological similarities between MTSCC and papillary renal cell carcinoma (RCC) with sarcomatoid changes may sometimes set forth some diagnostic difficulties. Papillary RCC, the second most common renal cell carcinoma subtype comprising 11% to 18%, has a proclivity for lymph node metastasis in 7% of cases and overall 5-year survival rate of approximately 86%. Sarcomatoid or spindle cell dedifferentiation is reported in 3% to 5% of papillary renal cell carcinoma and is a strong indicator for adverse prognostic outcome with 1-year and 5-year survival of 59% and 22%, respectively. Thus, the accurate pathologic distinction of mucinous tubular and spindle cell carcinoma from papillary renal cell carcinoma with sarcomatoid change is absolutely critical. The spindle cells of mucinous tubular and spindle cell carcinoma have low-grade nuclei, whereas the spindle cells in sarcomatoid papillary renal cell carcinoma have high-grade pleomorphic nuclei.[11]

Immunohistochemistry reveals a wide spectrum of positive markers and may help in the differential diagnosis. Thus, 93% of MTSCC shows a high expression of AMACR with strong granular cytoplasmic reactivity similar to that observed in 70% of papillary RCC. Both MTSCC and papillary RCC show high CK7 and EMA. Therefore, CK7 and EMA, like AMACR, are of no value in differentiating MTSCC and papillary RCC. CD10 is expressed in 93% to 100% of papillary RCC. In contrast only 15% of the MTSCC displayed immunoreactivity with CD10.[11]

Studies have shown that MTSCC is cytogenetically distinct from papillary RCC. Chromosomal gains, particularly in chromosome 7 and 17, and the loss of chromosome Y characterize papillary RCC. Fluorescent in situ hybridization studies have failed to show the chromosome 7 and 17 abnormalities in MTSCC. On the other hand, multiple genetic alterations involving losses in chromosomes 1, 4, 6, 8, 9, 13, 14, 15, and 22 are present in MTSCC.[11]

Low-grade collecting duct carcinoma (CDC), low-grade variant of medullary CDC, metanephric adenomas, chromophobe RCC, and renal tubulopapillary adenomas may also enter the differential diagnosis. MTSCC lack the characteristic morphologic features seen in classical low-grade CDC, such as infiltrative growth, cystic components, pleomorphic cells with significant nuclear atypia, desmoplasia, and intratumoural neutrophilic inflammation. Low-grade variants of medullary CDC are low-grade mucinous tumours with a solid and cystic architectures.[12] Metanephric adenomas, which are frequently reported in women, may display areas with tubular or acinar growth patterns. However, there are additional histologic findings such as papillary growth or psammoma bodies that may help. About 50% of cases also contain glomeruloid bodies, and most cases show an absence of immunohistochemical staining for EMA.[8,12] Chromophobe renal cell carcinoma comprises about 5% of epithelial renal neoplasms. Microscopically, it is composed of variably-sized cells with abundant pale reticular or flocculent cytoplasm. The nuclei are moderately sized and hyperchromatic. Bi- and multinucleated cells are not uncommon. The cytoplasmic density is greater at the periphery of the tumor cells in chromophobe RCC making the cytoplasmic borders thick and distinct.[1] Renal tubulopapillary adenomas may rarely present with an entirely tubular growth pattern, and most cases display at least focal papillary growth patterns and frequently contain psammoma bodies. Moreover, tubulopapillary adenomas are small lesions that rarely exceed 5 mm.[12]

Finally, in the absence of significant atypia, great caution must be exercised in the interpretation of sarcomatoid papillary RCC, especially in small biopsy samples, because it may resemble MTSCC. Although MTSCCs are thought to be low-grade tumors, with only rarely reported metastases, worrisome features such as atypia and necrosis may occasionally be observed. Pathologists must be aware of the spectrum and morphologic variability within MTSCC to ensure their accurate diagnosis.

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