Case Report

Clear cell changes in mucinous tubular and spindle cell carcinoma: cytoplasmic pallor/clearing within tubules, vacuoles or hybrid conventional clear cell carcinoma of kidney?

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Abstract: Mucinous tubular and spindle cell carcinoma (MTSCC) is a rare and recently recognized subtype of renal cell carcinoma (RCC). Apart from the classic morphology comprising conventional three components, there exist a large number of non-classic morphological variants of MTSCC, which make it necessity to differentiate from other RCC. Herein, we report two non-classic morphological variants of MTSCC. Case 1, a 85 years old man, showed numerous vacuoles among inherent components and cytoplasmic pallor/clearing within tubules mimicking conventional clear cell RCC with a 8.5 years follow-up, while Case 2 indicated a “mucin-poor” MTSCC associated with simultaneous conventional clear cell RCC at her age of 73 years. Until now Case 1 carries the longest disease-free survival reported in literature since MTSCC was defined and ranks the oldest since reported in literature, while Case 2 is the first report of “mucin-poor” MTSCC associated with simultaneous conventional clear cell RCC. Now, since no biomarkers or imagining tools but pathological examination can confirm the diagnosis of MTSCC, the management is always following the guideline of RCC in clinical practice. Generally, most reports consider it as a good prognosis disease, but sarcomatoid variant, even classic subtype can progress rapidly to life-threatening disease.

Keywords: Mucinous tubular and spindle cell carcinoma of the kidney, clear cell carcinoma, therapy, prognosis

Introduction

Mucinous tubular and spindle cell carcinoma, initially described (the first series) in 1998 [1], is a recently recognized subtype of renal cell carcinoma (RCC). Apart from the classic morphology comprising conventional three components, there exist a large number of non-classic morphological variants of MTSCC, which make it necessity to differentiate from other RCC. Herein, we report two non-classic morphological variants of MTSCC. Case 1, a 85 years old man, showed numerous vacuoles among inherent components and cytoplasmic pallor/clearing within tubules mimicking conventional clear cell RCC with a 8.5 years follow-up, while Case 2 indicated a “mucin-poor” MTSCC associated with simultaneous conventional clear cell RCC at her age of 73 years. Until now Case 1 carries the longest disease-free survival reported in literature since MTSCC was defined and ranks the oldest since reported in literature, while Case 2 is the first report of “mucin-poor” MTSCC associated with simultaneous conventional clear cell RCC. Now, since no biomarkers or imagining tools but pathological examination can confirm the diagnosis of MTSCC, the management is always following the guideline of RCC in clinical practice. Generally, most reports consider it as a good prognosis disease, but sarcomatoid variant, even classic subtype can progress rapidly to life-threatening disease.
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**Case reports**

**Case 1**

A 85 years old man who presented with flank discomfort and hematuria was referred to performed a Computed tomography (CT). CT scan showed a solid mass and a small cystic mass in the retroperitoneum arising from the left kidney. Plain CT showed a low homogeneous density lesion (30 HU, 3.5 × 3.28 cm) relative to renal parenchyma, without any cystic change and calcification (Figure 1A). Contrast-enhanced CT showed slight homogeneous enhancement (50 HU) of the mass, without a clear boundary with adjacent renal parenchyma (Figure 1B). Few signs of vascular, adrenal or perinephric fat invasion were detected. The patients underwent left open radical nephrectomy, suffering a chronic obstructive pulmonary disease (COPD) and chronic iron-deficiency anemia (CIDA) deriving from peptic ulcer (Hb 95 g/l). The specimen received consisted of a left kidney with a 3 × 3.5 cm, predominantly cortical-based poorly circumscribed tumor arising from the upper part of the kidney. The tumor was variegated tan, yellow, and gray-white, focally extending into renal hilum and compressing the Gerota’s fascia and pelvis but not invading them. The calyces and the ureter were not involved by the tumor. The tumor was extensively sampled. Sections were fixed in 10% neutral-buffered formalin and processed for light microscopy via conventional methods. Routine processing for histologic examination included paraffin embedding, sectioning, and staining with hematoxylin and eosin. Sections prepared from the formalin-fixed, paraffin-embedded tissue blocks were also used for immunohistochemical analysis. Generally, the renal tumor had a uniform microscopic appearance composed of cuboidal tubular tissue and spindle cells embedded by mucinous stroma (Figure 2A). The tubules and cords were lined by round to cuboidal cells of relatively bland morphology. The low-grade cell was associated with amphophilic cytoplasm and small uniform nuclei (Figure 2B). There were abrupt transitions between tubular structures and spindled areas composed of similar cells (Figure 2A), which were banal-appearing and often arranged in short fascicles (Figure 2C). Mitoses were very rare and numerous small vacuoles mimicking clear cells (Figure 2C). Prominent aggregates of foamy macrophages around spindle cells were found between cuboidal cells (Figure 3A). Focal cytoplasmic pallor or deletion conveyed a clear cell change, with some morphologically identical to conventional RCC, which were found in no more than one-eighth of this series (Figure 3B and 3C). The tumor cells in the more typical MTSCC areas showed strong and diffuse positivity for CK19, CK7 (Figure 4A), CAM5.2, Vimentin (Figure 4B), E–Cadherin, AMACR (P540S) (Figure 4C), CD10. The tumor cells were diffusely and weakly positive for 34βE12. In addition, the Ki-67 stain was less than 5%. The RCC antibody, CK20, CD15 stains were negative. Primary antibodies were applied as described in Table 1 and the complete immunohistochemistry results were present in Table 2. The patient received regular outpatient follow-up, and no local recurrence or distant metastasis has been found 8.5 years after resection.

**Case 2**

A 63-year-old woman was referred for an abdominal ultrasonography when going for a medical examination. Ultrasound examination showed a retroperitoneal mass arising from the middle part of the left kidney, with no signifi-
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Figure 2. A: Typical MTSCC areas show tubules, cords and abundant myxoid stroma. There were abrupt transitions between tubular structures and spindled areas composed of similar cells. (H&E, 40). B: The tubules and cords were lined by round to cuboidal cells of relatively bland morphology. The low–grad cell was associated with amphophilic cytoplasm and small uniform nuclei (H&E, 100). C: The spindled areas composed of banal-appearing cells, which were often arranged in short fascicles. Numerous small vacuoles mimicking clear cells. Mitoses were very rare. (H&E, 100).

Figure 3. A: Prominent aggregates of foamy macrophages around tubules and cords. (H&E, 100). B&C: Clear cell changes of MTSCC with some partially morphologically identical to conventional renal cell carcinoma (H&E, 200 and 400).

Figure 4. A: Strong and diffuse CK7 positivity in the tumor. B: The positive staining of Vimentin in the kidney tumor. C: Immunopositivity for P504S.

cant vascularity demonstrable on Doppler ultrasound. There were no symptoms of hematuria, voiding dysfunction, flank pain, or weight loss. Subsequently, MR imaging was performed and confirmed the presence of a 2.9 × 2.2 × 2.8 cm well-marginated mass on her left kidney, with a homogeneous low signal on T1-weighted imaging (Figure 5A) and an intermediate to high signal on T2-weighted imaging (Figure 5B). After intravenous (IV) injection of the contrast medium, there was a diffuse enhancement and most of the lesion was hypovascular compared to the adjacent cortex (Figure 5C). On T1-weighted imaging, before and after contrast, a central small scar could be defined (Figure 5A and 5C). There were no signs of vascular, adrenal or perinephric fat invasion. The patient underwent a left retroper-
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Table 1. Primary antibodies and concentrations used for immunohistochemistry

<table>
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<tr>
<th>Antibodies</th>
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<th>Company</th>
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<tbody>
<tr>
<td>CK7</td>
<td>1:100</td>
<td>Dako, Glostrup, Denmark</td>
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<td>CK19</td>
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</tr>
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<td>PS04s</td>
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<td>Dako</td>
</tr>
<tr>
<td>RCC</td>
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<td>Dako</td>
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<tr>
<td>Ki-67</td>
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<td>Dako</td>
</tr>
<tr>
<td>34βE12</td>
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</tr>
<tr>
<td>Vimentin</td>
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<td>Dako</td>
</tr>
<tr>
<td>E-Cadherin</td>
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<td>Dako</td>
</tr>
<tr>
<td>CAM5.2</td>
<td>pre-diluted</td>
<td>GeneTech, Shanghai, China</td>
</tr>
<tr>
<td>CD10</td>
<td>1:50</td>
<td>Leica</td>
</tr>
<tr>
<td>CD15</td>
<td>1:30</td>
<td>Novocastra</td>
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Table 2. Immunohistochemical characteristics of the two case

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<tr>
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<td>++</td>
</tr>
<tr>
<td>34βE12</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>CK7</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>CK19</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>CK20</td>
<td>--</td>
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</tr>
<tr>
<td>Vimentin</td>
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<td>++</td>
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<tr>
<td>CD15</td>
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<td>CD10</td>
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<tr>
<td>RCC</td>
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<td>--</td>
</tr>
<tr>
<td>P504s</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>E-Cadhesin</td>
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<td>++</td>
</tr>
<tr>
<td>Ki-67</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
</tr>
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</table>
++ strong positive; + positive; – negative.

Table 1 and 2. The patient is currently alive and well, 8 months after surgery. The imagining and biochemical tests show no evidence of recurrence or metastasis.

Discussion

MTSCC accounts for no more than 1% of all the renal neoplasms with less than 100 cases reported so far in the literature [7-9]. It affects patients from 1 to 82 years old with a mean age of 58 years and has a strong female predominance (with a male to female ratio of 1:4) [10]. Our first case was 85 years old when confirmed pathologically and is still alive at almost 94 in spite of suffering COPD. The majority of these tumors are accidentally detected when abdominal imaging studies were performed due to other indications [11]. Occasionally, when the mass are large enough, the patients may present with flank pain or hematuria [2]. The size of MTSCC may range from less than 1.0 cm in diameter to more than 18.0 cm, the majority of which measure 2.0 to 4.0 cm in the longest axis [12].

The diagnosis of MTSCC is mainly based on histological and morphological grounds, and immunohistochemical studies may show mostly specifically positive for RCC marker antigen, Vimentin, CK7, and AMACR [7, 13, 14]. Histologically, the MTSCC are characterized by admixture of low-grade tubular cuboidal cells with array of banal-appearing spindle cells embedded in the mucinous background. There are abrupt transitions between this component
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Non-classic morphological variants of MTSCC include foamy macrophages, papillations or well formed papillae focal clear cells in tubules, necrosis, oncocytic tubules, numerous small vacuoles, heterotopic bone, psammomatous calcification, nodular growth with lymphocytic cuffing and neuroendocrine differentiation [3-5]. Besides the inherent components, Case 1 showed numerous small vacuoles and focal cytoplasmic pallor or deletion within tubules morphologically identical to conventional clear cell RCC, while Case 2 indicated a “mucin-poor” change associated with simultaneous conventional clear cell RCCs. Actually, cells with optically clear cytoplasm are most commonly associated with clear cell RCC. Despite the cytoplasm in MTSCC is typically minimal and eosinophilic [2, 15], cytoplasmic pallor/clearing within tubules (no less than four cases [3, 16]) and numerous small vacuoles (no less than three cases [3, 6]) may focally present a “clear cell” appearance in these MTSCC. Therefore, several reports [3, 15, 17, 18] claimed that it is not sufficient to cause diagnostic confusion with clear cell RCC. The clear cell appearance of Case 1 had not been described before 2004 in our clinical center and it was considered not to be clear cell RCCs but small vacuoles and cytoplasmic pallor/clearing within tubules. However, apart from the typical morphologic characteristics of the clear cell RCCs, the neo-plasm of clear cells account for a large part of the mass in Case 2, which in all lead to the diagnosis of a hybrid tumor of MTSCC. Until now 2 cases of MTSCC associated with extensive clear cells either resembling [4] or morphologically identical to [19] clear cell RCC have been reported. Hes O and colleagues described it as a hybrid tumor [19], while Kuroda N and colleagues [4] claimed that foci of clear cells should be added to the histological spectrum of MTSCC. But, some researchers [3] believed that cases showing overall architecture of MTSC, but with definitive areas typical of clear cell RCC are currently best designated as “unclassified”, until the origin and long-term biologic potential of the tumors is better understood. However, it is possible that other diseases (including other renal mass) may coexist with MTSCC, as evidenced by 2 case with angiomyolipoma [3, 16], 5 cases with renal cysts [6, 16, 20] including ours, 1 case of papillary RCC [20], no less than 5 cases with nephrolithiasis including one case in our report [16, 19]. The real connection between MTSCCs and concomitant other RCCs has not been interpreted clearly.

Meanwhile, Case 2 presented a “mucin-poor” appearance (apart from the “clear cell” area). To date no less than 8 cases of MTSCC of this variation have been reported [3, 9]. Fine SW and colleagues [3] reported the morphology of 7 mucin poor of 17 MTSCC cases, with equal tubular and spindled areas (n = 4), spindle cell predominance (n = 2), or tubular predominance (n = 1). Farghaly H and colleagues [9] described that approximately 95% of their case was composed of spindle cell carcinoma cells. However, despite it is spindle cell predominance in Case 2, the mucin is quite poor (<1% of all components of MTSCC) in all slices. As most regard the typically abundant extracellular matrix as a key to MTSCC diagnosis [18, 19, 21], its absence makes accurate diagnosis of this entity more challenging.

Figure 5. A: MR imaging confirmed the presence of a 2.9 × 2.2 × 2.8 cm well-marginated mass on left kidney, with a homogeneous low signal on T1-weighted imaging. B: An intermediate to high signal on T2-weighted imaging. C: After intravenous (IV) injection of the contrast medium, there was a diffuse enhancement and most of the lesion was hypovascular compared to the adjacent cortex. On T1-weighted imaging, pre- and postcontrast, a central small scar could be defined.
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Figure 6. A: “mucin-poor” MTSCC exhibits tubules, cords and limited myxoid stroma. (H&E, 40); B: “mucin-poor” MTSC with elongated to serpentine tubules. The tubular structures were lined by low-grade of cell of flattened, sparse cytoplasm and regular elongated nuclei, which merge gradually to banal-appearing spindle-shaped with lightly eosinophilic cytoplasm. The nuclei were small, spherical and regular (H&E, 100). C: Limited myxoid stroma was observed in the center of the picture (H&E, 200). D: The transitions between the two components were abrupt (H&E, 200).

Figure 7. A: Tumor cells containing clear cytoplasm that exhibited histological features similar to clear cell carcinoma adjacent to the inherent components of MTSCC in the right of the picture. (H&E, 100). B&C: Nuclei were generally round and centrally located. Single distinct nucleoli were occasionally seen. Nuclear pleomorphism or abnormal mitotic figures were occasionally identified. The renal cell carcinoma component was of grade II-III of Fuhrman’s grading system (H&E, 100 and 400).

Figure 8. A: Strong and diffuse CK7 positivity in the tumor. B: Positive staining of Vimentin in the kidney tumor. C: Immunopositivity for P504S.

ed that the three components are present in variable proportions, with one or two predomina-

nance and individual cases of MTSCC may show uniform spindle cells with bland nuclear features, but lack in cords/tubules and mucinous background [22], so we are inclined to consider it as “mucin-poor” change of MTSCC in spite of being concomitant other non-classic variants. It is, therefore, critical for pathologists to recognize that “mucin-poor” variants of MTSCC exist.

Because of the rarity and recent description of MTSCC, few reports have focused on the treat-
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Despite that MTSCC is a rare renal lesion, the majority of MTSCC have a favorable prognosis [6]. However, to date no less than 8 cases have been went through recurrence [18], metastasis to regional lymph nodes [6, 13, 19, 25], or distant metastasis [10, 13, 25, 26]. About six case have been dead since reported [6, 10, 13, 14, 19, 26] with a follow up from 3 week to 5 years, four of them dying from distance metastasis [10, 13, 14, 26], one case dying from unrelated condition [19], and one case dying from unknown reason [6]. Sarcomatoid transformation reflects areas of high-grade dedifferentiation in renal epithelial tumors and generally indicates a worse prognosis with shorter disease-free survival and earlier, more frequent metastasis [27]. Four [10, 13, 14, 18] of the six reported cases [10, 13, 14, 18, 28] of sarcomatoid change in RCC have been described to be outgo through recurrence, regional lymph nodes metastasis or distance metastasis, three [10, 13, 14] of which have been dead since reported, with a follow up of 3 weeks to 9 month. In spite of the case alive reported by us, the prognosis is still unclear for clear cell change of MTSCC or MTSCC with clear cell morphologically identical to conventional clear cell RCC. Hes O and colleagues [19] reported a case of MTSCC with clear cell morphologically identical to conventional clear cell RCC. Lee J-H and colleagues [26] reported a common subtype of MTSCC which developed multiple metastatic pulmonary nodules 2 months after resection, then was found to have the left supraclavicular, right hilar and right subcarinal lymph nodes metastasis four months after the surgery and the patient died from respiratory failure 13 months after the operation. The prognosis data of other variants of MTSCC is relatively poor.

In summary, we have reported two cases non-classic morphological variants of MTSCC. Case 1 showed numerous vacuoles among inherent components and cytoplasmic pallor/clearing within tubules mimicking conventional clear cell RCC with the longest follow-up since MTSCC was defined, while Case 2 was the first report of a “mucin-poor” MTSCC associated with simultaneous conventional clear cell RCC. The cur-
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rent study also enriches the information of the management and the prognosis of MTSCC.

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Disclosure of conflict of interest

None.

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