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Case Report

Sarcomatoid change associated with epithelial-mesenchymal transition in mucinous tubular and spindle cell carcinoma of the kidney: a case report

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Abstract: We report an unusual case of mucinous tubular and spindle cell carcinoma (MTSCC) with sarcomatoid change in an 80-year-old Japanese male. In a resected specimen, a grayish-white tumor was found in the left kidney, and several metastases were observed in the right cervical bone and liver. Histologically, most of the main tumor examined showed MTSCC with sarcomatoid change. The transitions between the MTSCC and sarcomatoid components suggested that sarcomatoid transformation had occurred in the MTSCC. Immunohistochemically, the epithelial-mesenchymal transition (EMT)-associated marker ZEB1 was expressed in the sarcomatoid and transitional components. In contrast, ZEB1 expression was negative in the MTSCC component. The present findings support the view that MTSCC with sarcomatoid change represents MTSCC that develops a sarcomatoid component via EMT of the MTSCC component. EMT plays an important role in sarcomatoid change; thus, we conclude that MTSCC with sarcomatoid change is an 'EMT associated tumor'.

Keywords: Epithelial mesenchymal transition, mucinous tubular and spindle cell carcinoma, renal cell cancer, ZEB1, sarcomatoid change

Introduction

Renal cell carcinoma (RCC), the most common renal cancer among elderly individuals, generally originates from renal tubules, particulary the proximal tubule. Among the 13 histological subtype of RCCs, clear-cell renal cell carcinoma (ccRCC) is the most common. Mucinous tubular and spindle cell carcinoma (MTSCC) is a rare subtype that was recently classified, predominantly occurs in females, and is associated with a favorable prognosis. Although the origin of this tumor is unclear, it has been hypothesized to originate from the loop of Henle or the distal tubule [1]. The histopathological findings have been well characterized, and include interconnecting tubular and spindle cells with low-grade nuclear atypia and mucinous extracellular matrix.

In RCC, sarcomatoid features are observed in 5% of tumors [2]. These histological changes are commonly observed in chromophobe RCC and ccRCC [3]. Rarely, sarcomatoid change occurs in MTSCC; a small number of cases of MTSCC with sarcomatoid change have been reported [4-7]. The prognosis of RCC with sarcomatoid change is remarkably cruel; the presence of sarcomatoid change is regarded as a very poor prognostic factor [3, 4].

According to a recent report, sarcomatoid carcinoma is considered to result from sarcomatoid change of carcinoma cells; such sarcomatoid change might arise from epithelial-mesenchymal transition (EMT) [8]. EMT is characterized by a loss in cell polarity and changes in cell shape from cuboidal to fibroblastoid, the downregulation of epithelial markers, and the upregulation of mesenchymal markers. A hallmark event in EMT is the downregulation or loss of E-cadherin adhesion protein expression [9]. At the transcriptional level, E-cadherin is repressed by a number of nuclear factors (E-cadherin

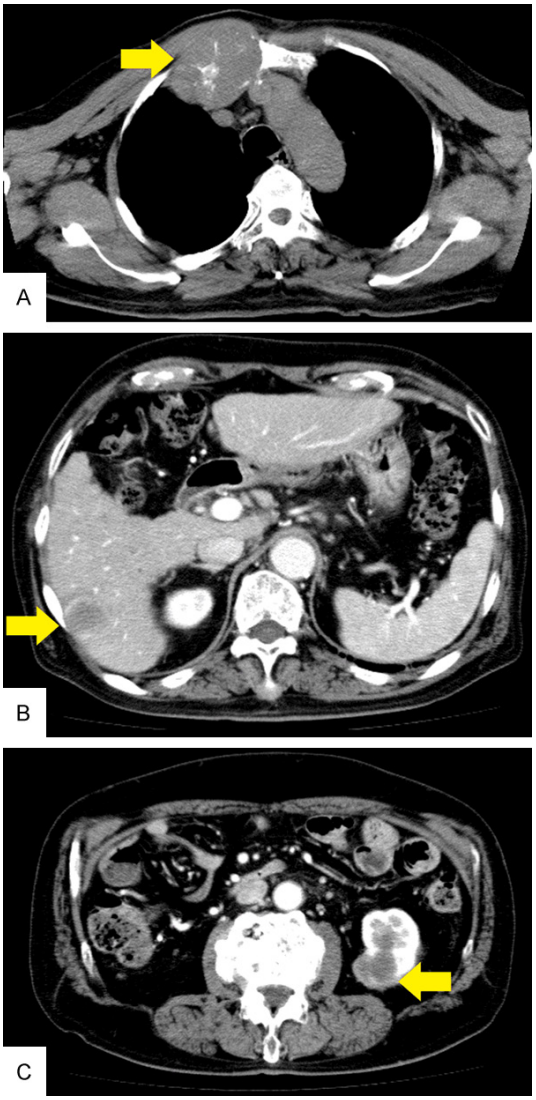

Figure 1. A. Axial CT image showing a heterogeneous mass on the right clavicle (arrow). B. Axial contrast-enhanced CT showing a low-density mass on the right hepatic lobe (arrow). C. Axial contrast-enhanced CT showing a low-density mass on the left kidney (arrow).

transcriptional repressors [EcTRs]), including ZEB1 (δEF1, ZFHX1A), ZEB2 (SIP1, ZFHX1B), SNAI1 (SNAIL), SNAI2 (SLUG), E12/E47, and TWIST. Expression of these EcTRs in tumor epithelial cells is inversely correlated with E-cadherin expression and associated with increased invasiveness/metastasis and poorer clinical prognosis [10].

In RCC, EMT plays an important role in the tumorigenesis of carcinoma with sarcomatoid change. Herein we report a rare case of MTSCC with sarcomatoid change that developed via EMT.

Case report

An 80-year-old Japanese man presented with discomfort and a palpable 3-cm mass in the right collarbone. Laboratory examination did not indicate increased levels of cancer-specific markers. Contrast-enhanced computed tomography (CT) revealed expansive lesions that involved the inferior pole of the left kidney, liver, and right clavicle, the largest of which measured 3 × 3 cm in diameter (**Figure 1A-C**). Pathological diagnosis of the right collarbone biopsy was papillary adenocarcinoma, which did not rule out metastatic papillary RCC. Therefore, the patient underwent partial nephrectomy.

Pathological findings

Grossly, the nephrectomy specimen had a 3.0 × 3.0 × 2.5-cm, predominantly cortical-based, poorly-circumscribed tumor. Macroscopically, no perinephric fat invasion was observed. The cut surface of the tumor appeared greyish-white and focally tan colored. Histologically, the tumor was composed of two components. The first histological component consisted of tubular structures lined by cuboidal cells with small nuclei, accompanied by spindle cells with low-grade nuclei, corresponding to a typical MTSCC component, comprising approximately 40% of the tumor area (**Figure 2A**). This component was accompanied by Alcian-blue (pH 2.5)-positive mucinous extracellular matrix. Mitoses were very rare in this area. The second histological component was composed of proliferating high-grade spindle cells with mucinous extracellular matrix. Mitotic figures were frequently observed (2 mitoses/10 high-power fields [HPFs]). This component corresponded to the sarcomatoid component (**Figure 2G**). A transition between the MTSCC and sarcomatoid components, showing the transformation from the tubular component into high-grade spindle cells, was observed (**Figure 2D**). Vessel and lymph vessel invasion were not prominent in either component.

Immunohistochemical staining was performed on formalin-fixed, paraffin-embedded sections using CK7 (OV-TL, DAKO, USA), EMA (E29, DAKO, USA), 34βE12 (34βE12, DAKO, USA),

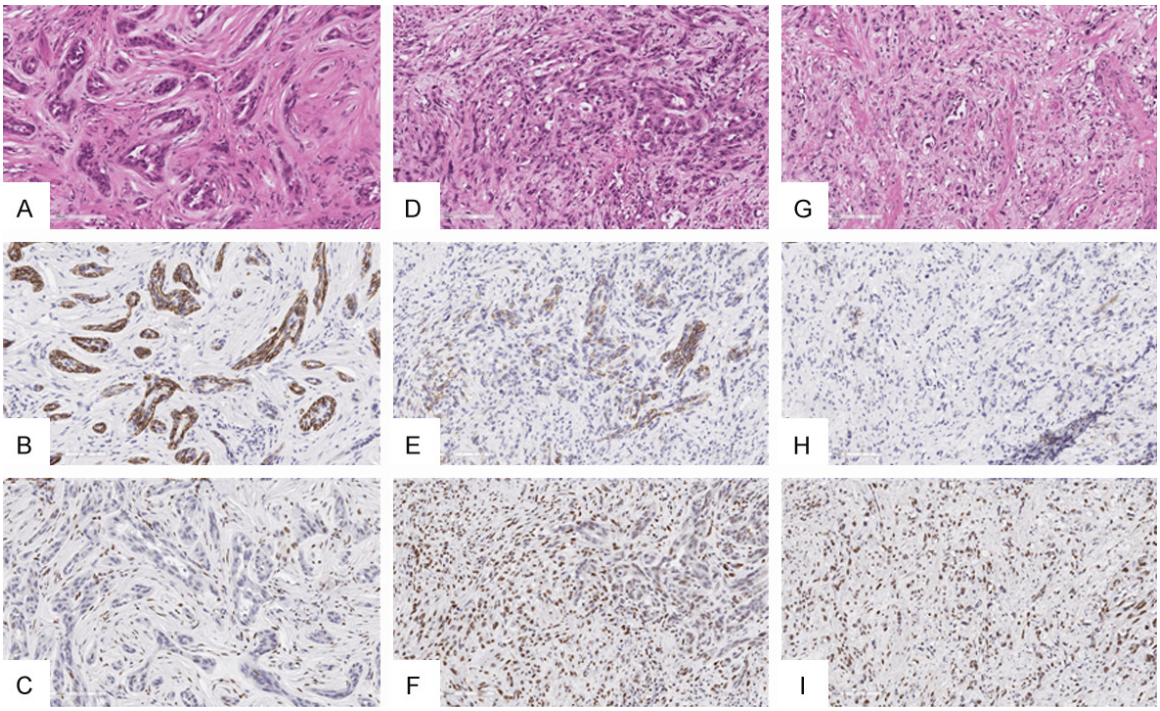

Figure 2. A. Microscopic view of the more typical MTSCC component (× 200, hematoxylin and eosin). B. E-cadherin immunohistochemical staining in the MTSCC component: expression is observed in the tubular glands (× 200). C. ZEB1 immunohistochemical staining in the MTSCC component: no expression is observed in the tubular glands (× 200). D. Microscopic view of the transition component, including the MTSCC component and sarcomatoid component (× 200, hematoxylin and eosin). E. E-cadherin immunohistochemical staining in the transition component: expression is observed in the tubular glands, and no expression is seen in the spindle cells (× 200). F. ZEB1 immunohistochemical staining in the transition component: expression is observed in the spindle cells and no expression is seen in the tubular glands (× 200). G. Microscopic view of the sarcomatous component with pleomorphic spindle cells (× 200, hematoxylin and eosin). H. E-cadherin immunohistochemical staining in the sarcomatous component: no expression is observed in pleomorphic tumor cells (× 200). I. ZEB1 immunohistochemical staining in the sarcomatous component: expression is observed in pleomorphic tumor cells (× 200).

CD10 (56C6, Novocastra Labo, UK), vimentin (Vim3B4, DAKO, USA), AMACR (13H4, DAKO, USA), E-cadherin (NCH-38, DAKO, USA), ZEB1 (polyclonal, SIGMA-ALDRICH, USA), Ki-67 (MIB-1, Immunotech.MBL, France), Slug (C19G7, Cell Signaling Technology, USA), and TWIST (Twist2C1a, Abcam, UK). All immunohistochemical stains were performed routinely in our laboratory using an auto-immunostaining system (Dako EnVision System, USA). The immunohistochemical staining profiles for each component are summarized in **Table 1**. Expression of the following markers differed between components: proximal tubule markers CD10 and AMACR; distal tubule markers CK7, EMA, and E-cadherin; and EMT-associated markers ZEB1, Slug, and TWIST. Furthermore, expression of the collecting duct marker 34βE12 was negative and that of the mesenchymal marker vimentin was positive in all components. The Ki-67 labeling index appeared as a hot spot in the MTSCC component; otherwise, it was higher in the sarcomatoid and transitional components.

The final pathological diagnosis was MTSCC with sarcomatoid change. Seven months after partial nephrectomy, the patient died due to multiple organ failure caused by peritonitis carcinomatosa and multiple metastases.

Discussion

MTSCC is a newly recognized, very rare subtype of RCC, and is generally considered to have a better prognosis than other RCCs [11]. Recently, MTSCC with sarcomatoid change was reported, and is associated with a very poor prognosis [10]. In the present case, sections through the entire tumor showed a MTSCC component, transition component, and sarcomatoid com-

Table 1. Summary of immunohistochemical findings

	MTSCC component	Transition component	Sarcomatoid component
CD10	+	+ weak	-
AMACR	+	+ weak	+
CK7	+	+	+
EMA	+ focal	-	-
E-cadherin	+	+ weak	-
34βE12	-	-	-
Vimentin	+	+	+
ZEB1	-	+	+
Slug	-	-	-
TWIST	-	-	-
Ki-67 LI (%)	10	30	30

CK = cytokeratin; EMA = epithelial membrane antigen; CD = cluster of differentiation; AMACR = α-methylacyl-CoA racemase; LI = labeling index; + = positive; - = negative.

ponent within the primary tumor. Direct transitions between the sarcomatoid component and MTSCC component in the primary tumor suggested that sarcomatoid change might have developed secondarily from pre-existing MTSCC components.

In recent years, EMT has been reported to be closely associated with tumor invasion, and metastasis is involved in the occurrence of carcinosarcoma in many organs [8, 12]. The expression of EcTRs, such as SNAIL, TWIST, and ZEB, results in repression of the epithelial phenotype and promotion of EMT, fibrosis, and metastasis. EcTRs are involved at multiple levels of transcriptional and post-translational regulation of E-cadherin [13]. During EMT, downregulation and loss of E-cadherin protein is important [9]. However, immunohistochemical results have suggested that among EcTRs, although ZEB1 is expressed in the sarcomatoid component, E-cadherin was not expressed. Furthermore, the relationship between E-cadherin expression and ZEB1 expression was inversely correlated with the MTSCC component and sarcomatoid component. This finding suggests the involvement of EMT in tumorigenesis. TWIST and SNAIL were not expressed in either component in this immunohistochemical study. These EcTRs are involved in the basic mechanisms of EMT. Moreover, each EcTRs represses E-cadherin expression through an independent pathway. Thus, ZEB1 expression in the absence of TWIST and SNAIL expression suggests EMT [13]. We conclude that EMT is involved in this tumorigenesis, and we propose that tumors associated with EMT during tumorigenesis should be called 'EMT-associated tumors'.

In a recent study, when compared with a cohort of patients with RCC without sarcomatoid change, those with RCC with sarcomatoid change tended to present at a more advanced stage [14]. Furthermore, patients with sarcomatoid change had a worse prognosis than did patients without sarcomatoid change. The patient in the present case died 7 months after surgery due to multiple organ failure caused by peritonitis carcinomatosa and multiple metastases. Pathologic distinction between mucinous tubular and spindle cell carcinoma from RCC with sarcomatoid component is imperative as it has important prognostic ramifications.

In conclusion, we have reported a rare, and to the best of our knowledge, the first, case of MTSCC with a sarcomatoid component associated with EMT.

Disclosure of conflict of interest

None.

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