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Low-grade metastases in high-grade clear cell renal cell carcinomas A clinicopathologic study of 4 cases with an insight into the role of mesenchymal-to-epithelial transition process

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ABSTRACT

Clear cell renal cell carcinoma (CCRCC) frequently develops distant metastases. However, high-grade primary CCRCC rarely leads to low-grade metastases. Cellular changes occurring during neoplastic progression known as epithelial-to-mesenchymal and mesenchymal-to-epithelial transitions explain this apparent contradiction. Four high-grade CCRCCs, which lead to low-grade metastases, are analyzed in this study, with the focus on epithelial-to-mesenchymal and mesenchymal-to-epithelial processes. Clinicopathologic data have been collected retrospectively and immunohistochemistry has been performed with E-cadherin, N-cadherin, vimentin, and WT-1. Three cases had organ-confined disease (2 pT2 and 1 pT1b). Three cases were G3 and 1 case was G4. Lung (3 cases), bone (2 cases), and pancreas (1 case) were the metastatic organs (2 patients developed multiple metastases). Metastases were G1 in all the cases. Average elapsed time between the primary tumor and the metastasis was 35.5 months. Three patients died of disease after 36, 120, and 180 months of follow-up, respectively. One patient is alive without disease after 75 months of follow-up. E-cadherin and N-cadherin showed concordant immunostaining patterns between primaries and metastases but inverse when correlated with Fuhrman grade. Hence, E-cadherin was positive in G3 cases and negative in G4, whereas N-cadherin was negative in G3 and positive in G4. Vimentin was positive in primaries and metastases only in 2 cases. WT-1 was consistently negative in all cases. In conclusion, pathologists must remember that high-grade CCRCC may develop low-grade metastases. Cadherin switching seems to be related to Fuhrman grade in this group of cases. This preliminary observation must be confirmed in longer studies.

1. Introduction

Renal cancer is a common neoplasm in Western countries. Actually more than 61 000 new cases are expected in the United States in 2015 [1]. Clear cell renal cell carcinoma (CCRCC) is by far the most common histologic subtype, ranging from 63% to 88.7% of all renal cell carcinomas in most series [2]. Traditionally resistant to radiotherapy and chemotherapy, surgery remains as the unique therapy with significant impact on survival [3]. The implementation of modern targeted therapies, although promising, is at present of limited use in daily routine due to the proved temporal and spatial intratumor heterogeneity that CCRCCs typically harbor [4].

A significant number of CCRCCs develop distant lymphatic and/or hematogenous metastases along its evolution [3,5]. Decades ago, a large autopsic study demonstrated that the probability of developing hematogenous dissemination in renal carcinomas is around 90% once lymph node metastases have appeared [6]. In this metastatic context, the prognostic impact of classical histologic features in the primary tumor diminishes or disappears and prognostic models turn to the prediction of response to systemic therapy [7].

Multiple comparisons between the primary and metastatic tumors have been performed in CCRCC [3,5,8–10]. However, the practicing pathologist's daily experience with CCRCC is sometimes shaken by a paradox: the primary CCRCC is a high-grade tumor, whereas its distant metastases are low-grade tumors. The present article intends to shed some light to this apparent contradiction analyzing the epithelial-to-mesenchymal (EMT)/mesenchymal-to-epithelial (MET) processes in 4 of such patients. The study has been performed by immunohisto-

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Table 1
Clinicopathologic data.

Case	Age (y)	Sex	Diam	pT	Grade	Sarc	Necrosis	Vasc Inv	Met site	Elapse	Grade	Treatment	Follow-up
1	59	F	7.2	2	3	No	No	No	Pancreas	60	1	No	DOD, 180
2	59	F	8	2	4	No	20%	No	Lung	63	1	No	DOD, 120
3	67	M	6.7	1b	3	No	No	No	Lung, humerus	10	1	No	AwoD, 75
4	69	F	8	3c	3	No	10%	Yes	Lung, vertebra	9	1	Sunitinib	DOD, 36

Abbreviations: AwoD, alive without disease; Diam, tumor diameter in centimeters; DOD, died of disease; Elapse, elapsed time between primary and metastasis; Met site, metastatic site; Sarc, sarcomatoid transformation; Vasc Inv, microscopic vascular invasion.

chemistry using 4 commercially available antibodies of widespread use, and the results are integrated with classic clinical and pathological data.

2. Materials and methods

Four high-grade (G3/4) CCRCCs that subsequently developed low-grade (G1) metastases have been retrospectively selected for this study. Clinical data were retrieved from the medical records and included age, sex, tumor diameter, surgical procedures, AJCC staging [11], elapsed time (months) between primary and metastasis, metastatic site, adjuvant therapies, if any, outcome, and follow-up (months). Histologic slides of both primary tumors and metastases were reevaluated regarding Fuhrman grade [12] and the presence of sarcomatoid transformation, tumor necrosis, and/or vascular invasion.

Immunohistochemical staining was performed in automated immunostainers (BenchMark Ultra; Ventana Medical Systems, Tucson, Arizona) following routine methods using vimentin (Roche, Ventana, reference 790-2917, prediluted), WT-1 (Roche, Ventana, reference 760-4397, prediluted), E-cadherin (Roche, Ventana, reference 790-4497, prediluted), and N-cadherin (Cell Signaling, reference 13116S, dilution 1:100) as primary antibodies. Tris-EDTA was used for antigen retrieval in all cases. Negative controls were slides not exposed to the primary antibody, and these were incubated in phosphate-buffered saline and then processed under the same conditions as the test slides. Positive controls were normal kidney and pancreatic tissues. The analysis was performed using a Nikon Eclipse 80i microscope (Tokyo, Japan).

To avoid misinterpretations due to regional heterogeneity, the area selected for immunohistochemical evaluation in every case was exactly that one in which Fuhrman grade had been previously assigned.

3. Results

Clinical data of the patients are summarized in Table 1. Cases were 3 women and 1 man with an average age of 63.5 years (range, 59-69 years). Two patients had multiple metastases. Lung (3 cases) was the most common metastatic site, followed by bone (2 cases; Fig. 1) and pancreas (1 case). The average elapsed time between the pathological diagnosis of the primary tumors and their metastases was 35.5 months (range, 9-63 months). Sunitinib was administered in 1 case. Three patients did not receive adjuvant therapy. Three patients died of disease after 36, 120, and 180 months of follow-up, respectively. One patient is alive without disease at the last contact, after 75 months of follow-up.

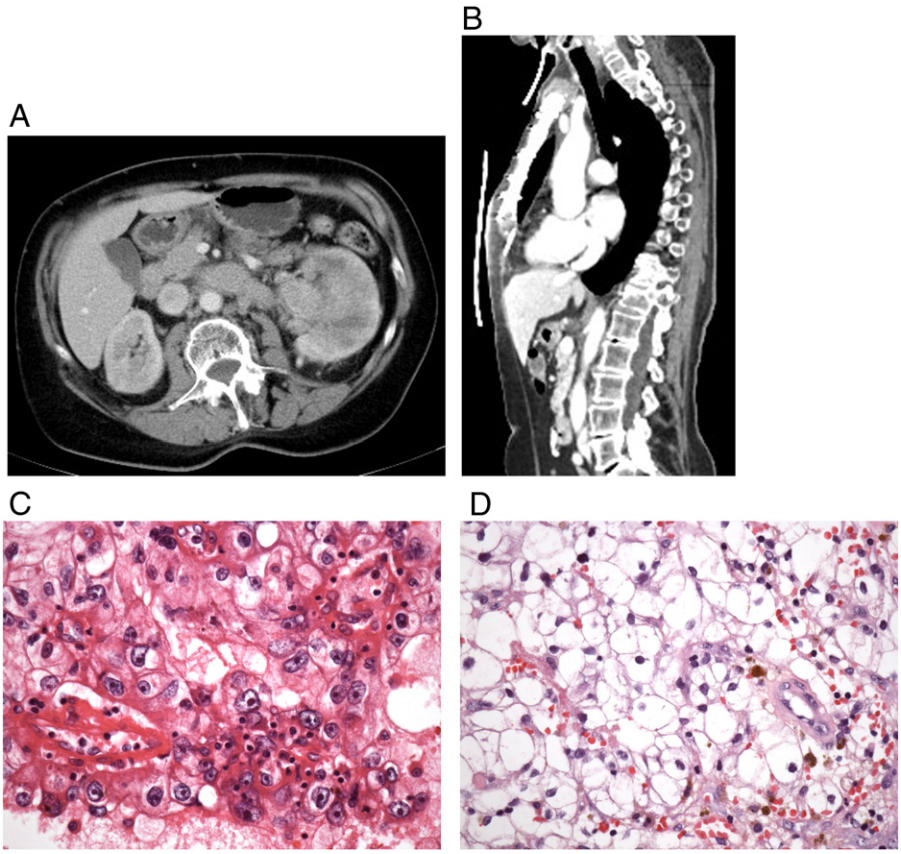

Fig. 1. Patient number 4: computed tomographic scans showing a large tumor mass with vein invasion in the left kidney (A) and vertebral metastases (B). Clear cell renal cell carcinoma was Fuhrman grade 3 in the primary tumor (C) and Fuhrman grade 1 in the metastases (D).