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Original contribution

Collecting duct carcinoma of the kidney: an immunohistochemical evaluation of the use of antibodies for differential diagnosis☆

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Summary Collecting duct carcinoma is a highly aggressive renal epithelial malignancy, although it accounts for less than 1% of the incidence of renal epithelial neoplasms. Differential diagnoses between collecting duct carcinoma, pelvic urothelial carcinoma with marked invasion to the renal parenchyma (invasive urothelial carcinoma), and papillary renal cell carcinoma is often challenging. In our current study, we examined the utility of using commercially available antibodies, in conjunction with lectin histochemistry, for such differential diagnoses. We examined 17 cases of collecting duct carcinoma, 10 cases of invasive urothelial carcinoma and 15 cases of papillary renal cell carcinoma (type 1, 6 cases; type 2, 9 cases) in these evaluations. Our results indicated that *Ulex europaeus* agglutinin 1, E-cadherin, and c-KIT were frequently positive in collecting duct carcinoma and invasive urothelial carcinoma, in comparison with papillary renal cell carcinoma, which had negative results for CD10 and α-methylacyl CoA racemase. We found, however, that collecting duct carcinoma showed positivity for high-molecular-weight cytokeratin and low-molecular-weight cytokeratin at a low frequency compared with invasive urothelial carcinoma, and that these distinctions need further careful evaluation. In addition, high-molecular-weight cytokeratin positivity was not a reliable marker for collecting duct carcinoma. We conclude that *Ulex europaeus* agglutinin 1 reactivity and positivity for E-cadherin and c-KIT are effective in distinguishing collecting duct carcinoma from papillary renal cell carcinoma, and that negative results for α-methylacyl CoA racemase and CD10 are potentially useful hallmarks of this distinction also. In contrast, a differential diagnosis for collecting duct carcinoma and invasive urothelial carcinoma will require careful examination of multiple routinely stained specimens, particularly in cases of in situ neoplastic lesions in the pelvic mucosa.
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1. Introduction

Renal epithelial neoplasms are composed of heterogeneous histologic subtypes, although clear cell renal cell carcinoma (RCC) accounts for approximately 80% of these

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cancers. Clear cell RCC comprises alveolar tumor cell architecture with a glycogen-rich clear cytoplasm and is associated also with sinusoid-like vasculature. Clear cell RCC has further been shown to harbor alterations in the *von Hippel-Lindau* tumor suppressor gene [1].

Papillary RCC accounts for approximately 10% of RCCs and is predominantly composed of papillary architecture lined with chromophilic tumor cells with fibrovascular cores. Papillary RCCs can be further classified into type 1 and type 2 tumors [2], and some harbor mutations in the *c-met* or *fumarase* genes. In addition, these lesions are often associated with familial occurrence, known as familial papillary RCC, and RCC-leiomyomatosis syndrome (for review, see Ref. [3]).

Chromophobe RCC and oncocytoma are derived from the intercalated cells of the collecting duct. The former is a low-grade malignancy, in spite of occasional sarcomatoid progression, whereas the latter is a benign tumor. These 2 lesions share various histologic and molecular biologic characteristics, and a differential diagnosis between them is therefore often challenging (for review, see Ref. [4]).

In addition to these subtypes, collecting duct carcinoma (CDC) has also been reported as a rare but aggressive subtype of renal epithelial neoplasm that is derived from the collecting duct. Although most cases of RCC can be successfully treated by surgical resection, CDC cases present with an unfavorable prognosis and often show postoperative recurrence and distant metastases [5]. In addition, the diagnostic criteria of CDC have not yet been fully established, which occasionally causes interobserver diagnostic discrepancies. Consequently, CDC is frequently difficult to distinguish from pelvic urothelial carcinoma with marked renal parenchymal invasion (invasive urothelial carcinoma [iUC]) and high-grade papillary RCC [6], although the World Health Organization recommends the use of the diagnostic criteria established by Srigley and Eble [7]. There are also several previous reports on the use of immunohistochemical markers for the differential diagnosis of these renal tumors, but some of these are not broadly used or commercially available yet [6]. In our present study, we examined the use of adopting such markers for the differential diagnosis of 17 cases of CDC, 10 iUCs, and 15 papillary RCCs.

2. Materials and methods

2.1. Renal epithelial cancer cases examined in this study

The renal epithelial neoplasm cases included in our present analyses were obtained from the consultation files of 2 of the authors of this study (O.M. and Y.N.) and dated from 1980 to 2000. To make a diagnosis of CDC, we adopted the criteria proposed by Srigley and Eble [7], except for reactivity with *Ulex europaeus* agglutinin 1 (*UEA-1*) and positivity for high-molecular-weight cytokeratin (HMW-CK), as we wished to reevaluate the efficacy of these markers. Only cases with a concordant diagnosis of CDC by O.M. and Y.N. were included in this study, and their pathologic stages were classified according to the UICC system [8]. iUC and papillary RCC were also diagnosed according to the World Health Organization classification system [9]. In cases of papillary RCC, only relatively well-demarcated, mass-forming lesions were included to avoid confusion with CDC. Papillary RCCs were classified as type 1 or type 2 according to Delahunt and Eble [2].

2.2. Histopathology and immunohistochemistry

Four-micrometer-thick, formalin-fixed, and paraffin-embedded tissue sections were stained with hematoxylin and eosin for routine histologic examination. The CDC and iUC tissue blocks that were subjected to immunohistochemistry were selected so as to cover the entire thickness of the lesion, i.e., from the pelvic mucosa to the perirenal fat. In cases of papillary RCC, blocks were selected to encompass the largest diameter of each tumor. Accordingly, 3 to 5 blocks were examined in each case of CDC, iUC, and papillary RCC. The histologic architecture associated with these renal lesions was described as papillary, microcystic, solid, and sarcomatoid, and the nuclear grades were classified according to the 4-graded system of Fuhrman et al [10]. The reagents used for lectin histochemistry and immunohistochemistry are listed in Table 1. The antibodies and lectins that we tested in this study were selected based on published reports and on our recent immunohistochemical analysis of renal neoplasms [2,3,6,9,13,15-19,21,27-31].

The staining procedures that we used were basically identical with those described in previous reports [11,12], except for several minor modifications. Briefly, the 4-μm-thick paraffin sections were deparaffinized and dehydrated. For lectin histochemistry, the sections were incubated with diluted biotinylated lectin solution at room temperature for 3 hours. The adsorbed lectin was then detected by incubation with peroxidase-conjugated streptavidin followed by a 3,3′-diaminobenzidine reaction. For immunohistochemistry, the sections were autoclaved in 10-mmol/L citrate buffer (pH 6.0) at 121°C for 15 minutes for antigen retrieval. After cooling, intrinsic peroxidase activity was quenched by immersing in 0.3% hydrogen peroxide/phosphate-buffered saline at room temperature for 30 minutes, followed by blocking with 10% normal rabbit or goat serum/phosphate-buffered saline. The sections were then incubated with the primary antibodies at 4°C overnight. The labeled antigens were detected with the HistoFine kit (Nichirei, Tokyo, Japan) and by 3,3′-diaminobenzidine reaction. For the immunodetection of E-cadherin and N-cadherin, the CSA kit (DAKO Cytomation, Kyoto, Japan) was used to amplify the signal. To assess the most appropriate tissue preparation for each antibody, nonneoplastic renal parenchymal tissue was

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