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ORIGINAL ARTICLE

Hybrid chromophobe renal cell neoplasm

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Abstract

Hybrid renal cell neoplasms (HRCNs) containing areas of tumor cells displaying cytological features of chromophobe renal cell carcinoma (CHRCC) and renal oncocytoma (RO) have been recently described in patients with renal oncocytosis and Birt–Hogg–Dube (BHD) syndrome (autosomal dominant genodermatosis). In this study, we identified cases of sporadic HRCN.

We reviewed 425 consecutive renal cell carcinomas (RCC), 18 CHRCC, six HRCN, and 25 RO.

Five HRCN were identified, including four from the group of RCC and two from RO. Patient age ranged from 40 to 68 years (mean age: 54 years), and the male:female ratio was 4:1. Tumors measured from 1.8 to 5 cm (mean diameter: 3.0 cm). Tumoral necrosis was not seen. Vascular invasion into medium-sized veins was identified in one HRCN. Chromophobe cells accounted for 20–80% of the tumors. Hale's colloidal stain showed weak to moderate diffuse cytoplasmic staining in scattered cells corresponding to those displaying routine staining features of chromophobe cells. Areas of oncocytic cells in studied tumors and control oncocytomas showed negative or focal cytoplasmic staining usually bordering extra- or intra-cytoplasmic lumina. Immunostaining for cytokeratin 7 and vimentin showed focal immunoreactivity in three cases and negative reactivity in all six cases, respectively. None of the study cases had microscopic RO, as commonly seen in renal oncocytosis, or were associated with BHD syndrome

Sporadic HRCN accounted for 1% of RCC. They were of smaller size than RCC and were associated with a favorable prognosis.

Introduction

Chromophobe renal cell carcinoma (CHRCC) accounts for about 5% of renal cell carcinoma (RCC) [24]. It is distinguished from clear cell RCC and papillary RCC by the characteristic chromophil cytoplasm seen with eosin or phloxin stain [23]. Cytogenetically, CHRCC is associated with various combinations of allelic loss of chromosomes 2, 6, 10, 13, and 17 [8,19]. Immunohistochemically, it shares lectin and immunological markers of the intercalated cells and oncocytoma [3,6,12,13,18,20]. Recently, hybrid renal cell neoplasm (HRCN), having an admixture of areas of CHRCC and areas consisting of oncocytes, have been described in patients presenting multiple renal oncocytomas (ROs) and Birt–Hogg–Dube (BHD) syndrome (autosomal dominant genodermatosis) [2,14,20,22]. In this study,

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Table 1. Summary of clinical and pathological features of study cases

#	Age	Gender	Tumor diameter	% of chromophobe cells	Associated with		VI	Follow-up
					CHRCC	RO		
1	45	M	2.5	30%				1 year, ND
2	56	M	1.8	20%	+	+		5 years, ND
3	40	M	2.5	80%			+	14 years, ND
4	62	F	5	60%				10 years, ND
5	68	M	3.5	45%				5 years, ND

M: male, F: female, VI: venous invasion, ND: no disease.

we reviewed cases of renal epithelial neoplasms at our institution to identify cases of sporadic HRCN and to study the clinical behavior of this entity.

Materials and methods

Files at the Anatomical Pathology Laboratory of the Ottawa Hospital, from 1983 to 2002, and General Campus, from 1999 to 2002, were reviewed to identify HRCN. Oncocytic cells were defined as tubular cells having prominent abundant granular eosinophilic cytoplasm. CHRCC was diagnosed using mainly the current cytoplasmic criteria with H&E staining. The diagnosis was supported by their positive reaction with Hale's colloidal stain. Each surgical specimen was represented by 3–12 sections, stained with hematoxylin–phloxin–saffron or H&E. HRCN was diagnosed when single or groups of chromophobe cells were identified and accounted for more than 20% of the tumor mass represented by available microscopic sections. Due to the presence of "pale" cells and occasional oncocytic cells showing a peri-nuclear halo that may mimic chromophobe cells in RO and the frequent weakly positive staining for Hale's colloidal iron in chromophobe cells, we arbitrarily excluded cases having less than 20% "chromophobe-like" cells from the group of HCRN. The size of the lesions was taken from the gross description of the specimen after formalin fixation or by measurement of the lesion on the glass slide. One representative tissue block of each tumor was used for immunostaining. Immunostaining was done on the formalin-fixed tissue sections using the avidin–biotin peroxidase complex (ABC) method with an ABC kit (Vector Laboratories, Burlingame, CA, USA) for cytokeratin cytokeratin 7 (Dako dilution 1:200) and vimentin (Dako, dilution 1:100). Clinical follow-up of up to 17 years was available for the majority of cases. A *t*-test was performed to analyze the statistical significance of the results.

Results

There were 403 consecutive non-chromophobe RCC, 18 CHRCC, six HRCN, and 23 oncocytomas. CHRCC were characterized by chromophobe cells with conspicuous cytoplasmic membrane, ballooned, reticulated, or eosinophilic cytoplasm that had a decreased tinctorial staining as compared to the cytoplasmic membrane. Nuclear halo was frequently seen in tumor cells with eosinophilic cytoplasm. Nuclei frequently displayed varying degrees of "raisinoid" changes. Focal areas with features of oncocytoma were not seen. All oncocytomas were distinguished from CHRCC by the cytoplasm that was granular and eosinophilic with indiscernible cytoplasmic borders. Peri-nuclear halos were occasionally and barely seen in focal areas. Pale cells in oncocytomas were distinguished from chromophobe cells by the absence of the peri-nuclear halo and the distinct cytoplasmic borders.

For five HRCN, patient age ranged from 40 to 68 years (mean age: 54 years). The male:female ratio was 4:1. The tumors measured from 1.2 to 5.0 cm (mean diameter: 3.0 cm) in greatest diameter. Two HRCN were associated with CHRCC and oncocytomas (Table 1). All associated oncocytomas measured more than 1 cm in

Fig. 1–3. 1. Case 1: HRCN with a history of CHRCC and a synchronous RO. (A) A poorly delineated nodule formed by chromophobe cells in RO. (B) A high magnification of the transitional area between RO and nodule of chromophobe cells. Note the conspicuous cell borders, translucent cytoplasm, and large raisinoid nuclei of chromophobe cells (arrowhead) as compared with indistinct cell borders, dense or occasionally light cytoplasm (arrow), and round or oval nuclei smooth nuclear contour in RO. (C) Hale's colloidal iron stain showing positive staining in large cytoplasmic portions in the nodule of chromophobe cells and negative staining or focal cytoplasmic staining in RO cells (arrow). **2.** Case 3: HRCN predominantly formed by chromophobe cells (80% of tumor cells) with vascular invasion. (A) The tumor with thick capsule and vascular invasion. (B) An area of tumor with a mass of chromophobe cells and focus of chromophobe cells intermingled with oncocytic cells (arrows). (C) Hale's colloidal iron stain showing positive staining in chromophobe cells and negative staining in RO cells. **3.** Case 5: HRCN with 50% of chromophobe cells in the upper half of the photomicrographs. (A, B) Low and high magnification showing area of chromophobe cells and area of RO. (C) Hale's colloidal iron stain and immunostaining for cytokeratin 7′ showing positive staining in the chromophobe cell component and almost negative staining in RO cells.