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Chromophobe renal cell carcinoma with neuroendocrine differentiation/morphology: A clinicopathological and genetic study of three cases

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Abstract Chromophobe renal cell carcinoma (ChRCC) with neuroendocrine differentiation/morphology (NED/NEM) is exceedingly rare. We present three cases of ChRCC with NED/NEM, two of which showed positivity for neuroendocrine markers on immunohistochemical analysis. Patients ranged in age from 49 to 79 years (mean: 64.3 years). One of the three patients died of metastatic disease to multiple organs. Of the remaining two patients, one is currently alive without disease and the other is alive with disease. Histologically, all three tumors were composed of conventional ChRCC and NEM showed glandular and rosette formation. Immunohistochemically, tumor cells were positive for CK7, KAI1, E-cadherin, and c-kit in both ChRCC and neuroendocrine areas in three cases. CD56 and synaptophysin immunoreactivity were detected in two cases; in only the neuroendocrine area in one case and in both components in the other. Neuroendocrine granules were ultrastructurally observed at both neuroendocrine and conventional areas of ChRCC. Array comparative genomic hybridization (CGH) study indicated losses of chromosomes 1, 2, 6, 10, 17, 21, and Y in both conventional ChRCC and NED in one case. In addition, losses of chromosomes 1, 2, 4, 6, 9, 10, 13, 16p, 17, and 21 were observed in both

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components of the remaining one tumor. Furthermore, loss of chromosome 5 was identified only in the neuroendocrine area in this case. We concluded that the neuroendocrine area may reflect dedifferentiation within ChRCC. It is possible that losses of chromosomes 4, 5, and 16p may be involved in the neuroendocrine differentiation or progression of ChRCC.

1. Introduction

Chromophobe renal cell carcinoma (ChRCC) accounts for about 5% of total renal neoplasms. ChRCC is recognized as a distinct subtype of RCC with a relatively good prognosis compared to clear cell RCC. In contrast, tumors with sarcomatoid changes and perinephric invasion may show an aggressive clinical course [1,2]. Cytogenetically, losses of chromosomes 1, 2, 6, 10, 13, 17, and 21 are frequently noted in conventional ChRCC [3]. The gains of several chromosomes have been reported in sarcomatoid ChRCC [4]. Two cases of ChRCC with neuroendocrine differentiation (NED) have been reported [5,6]. It was suggested that the neuroendocrine area may occur as a result of dedifferentiation within ChRCC [5,6]. However, to our knowledge, there have been no reports regarding genetic alterations in ChRCC with NED. Here, we present two cases of ChRCC with NED and one case of ChRCC with neuroendocrine morphology (NEM), and discuss the clinicopathological findings and genetic alterations.

2. Materials and methods

Three cases of ChRCC with NEM were extracted for this study from 105 ChRCCs diagnosed in Kansai Medical University Hirakata Hospital (case 1) and Kochi Red Cross Hospital, including consultation files (cases 2 and 3; case 3 originated from Tonami General Hospital) between 2006 and 2013. Among these three cases of ChRCC with NEM, two showed positivity for neuroendocrine markers on immunohistochemical analysis. Therefore, a diagnosis of ChRCC with NED was made in these two cases (cases 1 and 2), while the third was diagnosed as ChRCC with NEM (case 3). One case (case 2) was described previously [6].

2.1. Morphology and immunophenotypic studies

For all formalin-fixed and paraffin-embedded (FFPE) renal tumors from nephrectomy, sections 3 μm thick were stained with hematoxylin and eosin (H&E). Representative blocks from each case were selected for immunohistochemical studies using the Ventana Autostainer Benchmark XT (Ventana Medical Inc., Tucson, AZ). Primary antibodies to the following antigens were employed: CK7 (OV-TL 12/30, 1:100; DAKO, Glostrup, Denmark), KAI1 (G2, 1:100; Santa Cruz Biotechnology, Santa Cruz, CA), CD117 (polyclonal, prediluted; Nichirei, Tokyo, Japan), E-cadherin (NCH-38, 1:100; DAKO), CD56 (1B6, prediluted; Nichirei), synaptophysin (27G12, prediluted; Nichirei), and chromogranin A (LK2H10, prediluted; Japan Tanner, Osaka, Japan). The primary antibodies were visualized using a Ventana I-VIEW DAB Universal kit (Roche Diagnostics KK, Tokyo, Japan).

2.2. Ultrastructural studies

Materials included in paraffin blocks from two cases (cases 1 and 2) were processed for transmission electron microscopy to evaluate the presence of neuroendocrine granules. Small sections were extracted from both conventional ChRCC and neuroendocrine areas. Specimens were deparaffinized, fixed in 2% osmium tetroxide, and embedded in epoxy resin. Ultrathin sections were cut with a Reichert microtome, stained with uranyl acetate and lead citrate, and examined with an electron microscope (JEM-1400A; JEOL, Tokyo, Japan). Micrographs were taken at different magnifications (×4000–×50000).

2.3. Genomic DNA extraction and array comparative genomic hybridization

Written informed consent was obtained from two patients (cases 1 and 2) for genetic studies. Genomic DNA was extracted from FFPE tissue samples as described previously [7]. The use of tissue samples for all experiments was approved by the Oita University Ethics Committee (approval no. 700) in accordance with the Ethical Guidelines for Clinical Research of the Japanese Ministry of Health, Labour and Welfare, 2008 (http://www.mhlw.go.jp/english/). The Agilent Human Genome Array CGH microarray 44K (Agilent Technologies, Palo Alto, CA) was used for array-comparative genomic hybridization (CGH) analysis. Genomic DNA was extracted from the tumor in both conventional ChRCC and neuroendocrine areas, and the non-tumor region from the