Chromophobe renal cell carcinoma, oncocytic variant: Cytological and ultrastructural observations

ABSTRACT
There is only one report on cytological findings of oncocytic variant of chromophobe renal cell carcinoma (RCC). In this article, we report a new case with focus on cytological, and ultrastructural findings. A 60-year-old Japanese man was found to have a right renal tumor on medical checkup. In imprint cytological materials, the smears consisted of slightly discohesive clusters and isolated tumor cells with granular green colored cytoplasm on Papanicolaou staining. Nuclei were generally round and centrally located in the cytoplasm, but nuclear irregularity or perinuclear halo was absent. Ultrastructurally, the tumor was full of mitochondria with tubulovesicular cristae. Fluorescence in situ hybridization study using histological material showed multiple chromosomal losses including chromosomes 7, 10, 13, and 17. This finding supports the hypothesis that this variant may ultrastructurally show the nature of chromophobe RCC rather than renal oncocytoma.

Key words: Chromophobe renal cell carcinoma (RCC), imprint cytology, imprint, oncocytic variant, ultrastructure

Introduction
The oncocytic variant of chromophobe renal cell carcinoma (RCC) has been recently proposed by our group.[1] To date, there are only five cases on this variant.[2] However, there is only one report on cytological findings and no descriptions on ultrastructural findings.[1,2] The differential diagnosis between oncocytic variant of chromophobe RCC and renal oncocytoma (RO) is important because of their different biological behavior. In this article, we report a new case of chromophobe RCC, oncocytic variant with the focus on cytological and ultrastructural findings.

Case Report
The abdominal ultrasound sonography on medical checkup in a 60-year-old Japanese man disclosed a right renal cystic tumor measuring approximately 30 mm in maximum diameter. Subsequent computed tomography (CT) scan and magnetic resonance imaging (MRI) also confirmed the right renal tumor. Preoperative laboratory examination showed no abnormal findings. No other obvious tumorous lesions were detected by systemic image screening. No symptoms of Birt–Hogg–Dubé syndrome were detected.

Laparoscopic right nephrectomy was also performed. The course of the patient was uneventful 22 months after the operation.

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Results

Macroscopic findings
The tumor measuring 30 mm × 25 mm × 25 mm with marked cystic change and focal solid area was observed in the upper pole of the right kidney. The cut surface of the tumor was brown in color.

Imprint cytological findings
The Papanicolaou stained smears showed slightly discohesive clusters and isolated tumor cells with granular cytoplasm staining green in color. The cytoplasm had slightly ill-demarcated borders. Nuclei were generally round, uniform, and centrally located in the cytoplasm, but nuclear irregularity, nuclear grooves of raisinoid nuclei, and perinuclear halo were absent [Figure 1]. Chromatin was finely granular, the nuclear rim was smooth, and the nucleoli were usually single and small. Occasionally, glandular cell clusters were seen and cytoplasmic vacuoles were also present. The background stroma possessed no foamy macrophages or necroses. No papillary clusters with fibrous vascular stalks were seen. These cytological findings corresponded to RO rather than chromophobe RCC. In immunocytochemical staining, tumor cells showed a diffuse positive reaction for cytokeratin 7 (CK7) and vimentin. However, CD10, CD117, and alpha-methylacyl-CoA racemase (AMACR) were completely negative.

Pathological findings
The tumor was well-circumscribed but encapsulated. The tumor consisted of tubular or cribriform growth pattern of cuboidal to low columnar cells with deeply eosinophilic cytoplasm [Figure 2]. Nuclei were uniformly round and centrally located, but irregular nuclei, raisinoid nuclei, nuclear grooves, and perinuclear halo were not seen. No nesting growth pattern in edematous or hyalinized stroma reminiscent of RO was seen. No perirenal fat invasion was identified, but the tumor invaded branches of renal vein. The tumor showed positivity along the luminal sides for colloidal iron stain. Immunohistochemically, tumor cells showed diffuse positivity for CK7, epithelial (E)-cadherin, antimitochondrial antigen (MIA), vimentin, epithelial membrane antigen (EMA), and CD82, but negativity for CD10, RCC marker (Ma), AMACR, melanosomes, and CD117. Fluorescence in situ hybridization (FISH) analysis of the tumor revealed monosomy of chromosomes 7, 10, 13, and 17. Ultrastructure studies showed numerous mitochondria with the cytoplasm of tumor cells. Cristae showed tubulovesicular pattern rather than lamellar pattern [Figure 3]. Intracytoplasmic microvesicles were not seen, but discrete lipid, glycogen granules, and low dense lysosomes were rarely observed.

Discussion
We recently proposed the disease entity of chromophobe RCC, oncocytic variant.[1] This tumor is characterized by the dominant tubular or cribriform growth pattern of oncocytic cells with centrally located nuclei and without perinuclear haloes and distinct cell border resembling RO. However, this tumor shows the diffuse positive for CK7, unlike RO. Cytogenetic findings show the feature of chromophobe RCC, namely multiple chromosomal losses.[1,2] In this case, the tumor had these features. Accordingly, we finally diagnosed this tumor as an oncocytic variant of chromophobe RCC. This tumor should be strictly distinguished from RO with renal vein invasion or sporadic hybrid oncocytic/chromophobe tumor.[3,4]
Ultrastructurally, most cases of chromophobe RCC with eosinophilic cytoplasm have mitochondria with tubulovesicular or tubulocystic cristae, whereas the majority of RO possesses lamellar cristae. However, ROs having mitochondria with tubulovesicular cristae have been reported. The cristae in this case showed a tubulovesicular morphology. The existence of tubulovesicular cristae in RO suggests that ultrastructural intermediate form between RO and chromophobe RCC actually exists. In mitochondria having tubulovesicular cristae in chromophobe RCC, a close relationship with microvesicles and mitochondria has been suggested. Tickoo et al. speculated that microvesicles might be derived from abnormal mitochondriogenesis. When abnormal mitochondriogenesis is none or mild in chromophobe RCC, we suggest that the tumor may show the oncocyic variant (numerous mitochondria and no to a small number of microvesicles). When it is moderate, the eosinophilic variant (moderate number of microvesicles and moderate number of mitochondria) should be considered. Furthermore, when it is severe, the typical variant (a large number of microvesicles and a small number of mitochondria) can be yielded. Therefore, we suggest that factors controlling normal or abnormal mitochondriogenesis regulate the histological subtype of chromophobe RCC. In this study, we found numerous mitochondria, of which the majority showed tubulovesicular cristae. The present case ultrastructurally had abundant mitochondria and no microvesicles, reflecting an RO-like morphology with deeply eosinophilic to oncocyic cytoplasm. However, we consider that this variant may ultrastructurally have characteristics of chromophobe RCC rather than RO on the basis of mitochondrial cristae morphology.

Regarding cytological findings, this variant shares many characteristics of RO including centrally located round nuclei and absence of perinuclear halo and smooth nuclear membrane. Unless cytopathologists or pathologists can recognize the tubular or cribriform architectures in cytological materials, it becomes very difficult to identify the oncocyic variant of chromophobe RCC. In this situation, FISH study using cytological material may be of use.

In summary, we report the second case with cytological descriptions of an oncocyic variant of chromophobe RCC. Mitochondrial morphology using an ultrastructural examination showed the nature of chromophobe RCC, namely tubulovesicular cristae.

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Conflicts of interest
There are no conflicts of interest.

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