Chromophobe Renal Cell Carcinoma with Osseous Metaplasia: a Case Report

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INTRODUCTION

The updated WHO histological classification offers a subdivision of renal cell carcinoma (RCC) by both their morphological and cytogenetic features into clear cell, granular cell, chromophobe cell, spindle cell, cyst-associated, papillary and collecting-duct carcinomas (1). Chromophobe cell carcinoma of the kidney is a recently recognized category of human RCC (2) that was initially described in nitrosomorpholine-induced experimental rat RCC by Bannasch et al. (3). At present, chromophobe RCC may account for about 5% of all cases of RCC. Cancer cells of this distinct type of RCC display a characteristic weak and cloudy cytoplasmic staining pattern imparting a reticular appearance with conventional hematoxylin and eosin stain, corresponding to a variable number of cytoplasmic microvesicles seen by electron microscopy. Genetically, it is characterized by a combination of loss of heterozygosity at chromosomes 1, 2, 6, 10, 13, 17 and 21 (4). Ultrastructural and immunohistochemical characterization have demonstrated the close phenotypic similarity between chromophobe RCC and intercalated cells of the renal collecting duct (5,6). Here we present a case of chromophobe RCC with osseous metaplasia within the tumor tissue.

CASE REPORT

CLINICAL SUMMARY

A physician incidentally found a tumor of the left kidney in a 60-year-old Japanese male by abdominal ultrasonography in the course of a routine check-up. Computed tomography (CT) and magnetic resonance imaging demonstrated a well-demarcated, solid tumor arising from the lower pole of the left kidney (Fig. 1). The tumor was subsequently removed by partial nephrectomy at the Department of Urology, Hiroshima General Hospital of West Japan Railway Company.

The patient has been followed up for 2 years by abdominal CT taken every 3 months after the surgery without any evidence of tumor recurrence or metastasis.
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PATHOLOGICAL FINDINGS

The resected tumor, measuring 18 × 27 mm, was well circum-
scribed with a fibrous capsule. The cut surface of the tumor
was brownish tan with focal hemorrhage. Necrotic area was
not observed. Paraffin sections from formalin-fixed material
were stained with hematoxylin and eosin, periodic acid–Schiff
(PAS), alcian blue (AB) and Hale’s colloidal iron. Immuno-
histochemical examination was undertaken using Vectastain
avidin–biotin peroxidase complex kit (Vector, Burlingame,
CA) and specific monoclonal antibodies against epithelial
membrane antigen (EMA) (Clone GP1.4), cytokeratin (Clone
5D3 and LP34) and vimentin (Clone VIM3B4) as described
elsewhere (7). Antibodies were purchased from Novocastra
(Newcastle upon Tyne, UK). Histologically, the tumor was
composed of solid cell sheets surrounded by delicate stroma
containing capillaries (Fig. 2a). The tumor cells had abundant
and cloudy cytoplasm imparting a reticular appearance with
accentuated cell membranes making up a plant cell-like
appearance. The nuclei were slightly pleomorphic with
coarsely granular chromat in and occasional prominent nucleoli
conforming to a grade 2 nuclear atypia (Fig. 2b). Periodic
acid–Schiff (PAS) staining demonstrated a fine and delicate
reaction to glycogen in comparison with heavy deposits
observed in ordinary clear cell carcinomas (not shown). The
cytoplasm of the tumor cells revealed a diffuse positive reac-
tion with Hale’s colloidal iron stain (Fig. 2c), which is a diag-
nostic feature for chromophobe RCC (2). The peripheral part
of the tumor underwent sclerotic fibrosis and focal osseous
metaplasia was found (Fig. 2d). The tumor cells revealed a
positive immunoreaction to EMA and cytokeratin, while
vimentin immunoreactivity was exclusively negative
throughout the tumor. Electron microscopy of the tumor cell
revealed numerous microvesicles within the cytoplasm (not
shown). These vesicles, round to oval in shape, were 200–400
nm in diameter and had a tendency to be concentrated adjacent
to and surrounding the nucleus.

DISCUSSION

Although limited data are available regarding the clinical
behavior of chromophobe RCC, it has been suggested that this
distinctive type of RCC has a relatively low malignant
potential compared with common type RCC (8,9). Histopatho-
logical characteristics of chromophobe RCC are a nesting
arrangement of the tumor cells with sharply defined borders
(plant-like appearance) and abundant pale acidophilic reticular
cytoplasm (2). Since the initial report by Thoenes et al. (2),
positive cytoplasmic reaction to Hale’s colloidal iron stain has
been considered to be a diagnostic feature for chromophobe
RCC and has been used as a discriminatory feature to differen-
tiate it from other renal tumors. However, it is noted that other
subtypes of renal cancer also show positive reaction to this
method with different staining patterns in comparison with that
described for chromophobe RCCs. Tickoo et al. (10) empha-
sized that the diffuse and strong reticular cytoplasmic stain
with Hale’s method, as was observed in tumor cells in the
present case, was highly characteristic of chromophobe RCC.
The presence of variable numbers of intracytoplasmic micro-
vesicles is an important electron microscopic feature of this
type of RCC (2). Bonsib and Lager (9) and Akhtar et al. (11)
suggested that these microvesicles may be derived from the
outer membranes of mitochondria through extensive
ultrastructural study. However, Tickoo et al. (12) could not
observe coarse granular cytoplasmic staining by antimitochon-
drial antibody 113–1, that recognizes a 60 kDa non-glyco-
sylated protein component of mitochondria, in typical
chromophobe RCC. Tumor cells of chromophobe RCC present
negative vimentin immunoreactivity, while demonstrating
positive immunoreaction to cytokeratin and EMA, as was
observed with the present tumor (13). This is also one of the
characteristic phenotypes of chromophobe RCC for distinction
from common-type RCCs. From these morphological observa-
tions, we concluded that the present tumor was compatible
with typical chromophobe RCC (8).

The unique histopathological finding of the present chromo-
phobe RCC is a focus of bone formation within the tumor.
Daniel et al. (14) reported that 10.3% (58/580) of renal cell

Figure 1. Medical imaging of the renal tumor. (a) Coronal images on dynamic
magnetic resonance imaging reveal a well-defined, solid tumor arising from
the lower pole of the left kidney with inhomogeneous enhancement. (b) Plain
computed tomography shows a small calculus within the tumor.
carcinomas had calcified foci through a roentgenographic review of 2709 renal masses at the Mayo Clinic. Moreover, reports on osseous metaplasia or bone formation within RCC with histopathological confirmation are rare (15,16). Although Akhtar et al. (11) described two cases of chromophobe RCC with radiologically validated calcification, substantially this is the first report on chromophobe RCC with histologically proven ossification. Because the ossified focus in the present case was found within the fibrotic area of the tumor apart from cancer cell nests, stromal osseous metaplasia could be the best explanation for the histogenesis (17).

Recent advances in cytogenetic and molecular biological analysis have disclosed the genetic background of each subtype of RCC (18). Speicher et al. (4) reported specific loss of chromosomes 1, 2, 6, 10, 13, 17 and 21 in chromophobe RCC by a comparative genomic hybridization method. On the other hand, common-type RCCs are genetically separated from others based on the occurrence of a highly specific deletion of chromosome 3p (19) with mutation of VHL gene (20).

Combination of histopathological examination and molecular cytogenetic analysis as was proposed by Bugert and Kovacs (21) may improve the accuracy of diagnosis of RCCs according to the new WHO classification in the near future.

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