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# Clinicopathology study of eight cases of chromophobe renal cell carcinoma

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Abstract :
The prognosis of chromophobe renal cell carcinoma (RCC) is generally favorable. However, some investigations argue against this point of view. In this article, we performed clinicopathologic study of eight cases of chromophobe RCC with focus on prognostic factors. The incidence of chromophobe RCC accounts for 7.3% of total renal tumors. In six patients, tumor was incidentally discovered. Aggressive form was observed in three patients who died of disease in one or showed the distant metastasis in two. Four tumors macroscopically showed more than 8 cm in maximum diameter, which all showed necrosis. Among these tumors, three tumors showed pathologically more than stage III, more than CTG 2, and vascular invasion. Two among these three tumors contained unusual morphological finding, namely neuroendocrine differentiation or breast cancer-like morphology. Five tumors showed CTG 1 and Stage I, which showed neither recurrence nor metastasis. Finally, several factors such as more than 8cm in maximum diameter, macroscopic necrosis, vascular invasion, more than CTG 2 and usual histologic features including neuroendocrine differentiation and mammary-like carcinoma may be worse prognostic indicators in chromophobe RCC.

Keywords : chromophobe RCC, clinicopathologic study, prognosis

## INTRODUCTION

The prognosis on chromophobe renal cell carcinoma (RCC) is debatable to date.[1-12] The Fuhrman grading system has been widely used in clear cell and papillary RCC and has been recently revised as ISUP grading system with special emphasis on nucleolar characteristics.[13,14] However, Fuhrman grade and revised ISUP grade are not applicable in chromophobe RCC.[14-17] Recently, Paner et al. proposed the new grading system, Chromophobe Tumor Grade (CTG) instead of Fuhrman nuclear grade.[18] However, the clinical and biological significance of CTG was controversial to date.[18-20] In this study, we performed the clinicopathologic study of eight cases with chromophobe RCC with special emphasis on prognostic factors.

## MATERIALS AND METHODS

Among surgically resected one-hundred nine renal tumors between January 2007 and December 2016, eight cases with chromophobe RCC has been selected in the present study. Two cases have been previously reported.[1-22] Clinical finding (sex, age, symptoms, imaging findings and clinical stage) macroscopic findings (color, necrosis, hemorrhage and cyst), microscopic findings (major subtype, other histologic features, Fuhrman Grade, CTG,

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vascular invasion, lymph node metastasis and pathological stage) and therapy/outcome were retrospectively examined for each case. CTG was evaluated according to the Paner's criteria.[18] Additionally, the progression-free survival of 7 cases with chromophobe RCC was compared with that of 24 cases with clear cell RCC diagnosed between 2010 and 2011, using Kaplan-Meier method and the long-rank test. All *P* values were two sided and a $P<0.05$ was considered to be significant.

## RESULTS

*Clinical features*

The clinical information is summarized in Table 1. Eight cases with chromophobe RCC accounted for 7.3% of one-hundred nine renal tumors surgically resected during this period. Patients consisted of five men and three women. The age of patients ranged from 42 to 80 years with a mean age of 63.8 years. In six patients, tumor was incidentally discovered. One patient presented with hematuria and another patient presented with weight loss. The dynamic computed tomography scan showed heterogeneous enhancement in four patients, homogenous enhancement in one patient and no enhancement in two patients. The imaging information of the remaining one patient was not available. The clinical stage was composed of five tumors in stage I, two in stage III and one in stage IV.

TABLE 1: Clinical summary

| Case | Sex | Age | Symptom | Enhance CT findings | cStage |
|---|---|---|---|---|---|
| 1 | M | 53 | incidentally found | ? | Stage I |
| 2 | F | 42 | hematuria | heterogeneous enhance | Stage IV |
| 3 | M | 80 | incidentally found | heterogeneous enhance | Stage I |
| 4 | M | 79 | weight loss | heterogeneous enhance | Stage III |
| 5 | M | 54 | incidentally found | homogenous enhance | Stage I |
| 6 | F | 74 | incidentally found | no enhance | Stage I |
| 7 | F | 68 | incidentally found | no enhance | Stage I |
| 8 | M | 66 | incidentally found | heterogeneous enhance | Stage III |

M, male: F, female.

TABLE 2: Summary of macroscopic findings

| Case | Size | Cut surface color | Necrosis | Hemorrhage | Cyst |
|---|---|---|---|---|---|
| 1 | 4cm | Beige | - | + | - |
| 2 | 8cm | Beige~light brown | + | + | - |
| 3 | 1.9cm | Beige~light brown | - | + | - |
| 4 | 22cm | Beige | + | + | - |
| 5 | 3.1cm | light brown | - | - | - |
| 6 | 8.5cm | light brown~beige | + | - | - |
| 7 | 4.5cm | Beige | - | - | + |
| 8 | 8.2cm | light brown~beige~yellow | + | + | - |

+, present; -, absent.

*Pathological findings*

*Macroscopic findings*

Macroscopic features are summarized in Table 2. The tumor size ranged from 1.9 to 22 cm with a mean size of 7.5 cm. The cut surface showed in beige or light brown to beige in all tumors, and one tumor additionally showed focal yellow area. Necrosis and hemorrhage were observed in four and five tumors, respectively (Fig.1). Cyst formation was identified in only one tumor.

*Microscopic findings*

Histologic features are summarized in Table 3. The major subtype consisted of five cases in typical variant (Fig. 2a) and three cases in eosinophilic variant (Fig. 2b). Additionally, nested or trabecular growth pattern (Fig. 2c) on the fibrotic stroma resembling mammary invasive carcinoma, NOS was seen in one tumor. Neuroendocrine differentiation (30%) (Fig. 2d) and sarcomatoid change (1%) (Fig. 2e) were observed in one tumor. Tumor cells showing pleomorphism, giant cells and bizarre nuclei (Fig. 2f) were noted in one tumor. Fuhrman grade consisted of five tumors in grade 2, one in grade 3 and two in grade 4. CTG was composed of five tumors in grade 1 (Fig. 2a, b), one in grade 2 (Fig. 2g) and two in grade 3 (Fig. 2e, f). Vascular invasion (Fig. 2h) was recognized in three tumors.

TABLE3: Summary of microscopic findings

| Case | Variant | Other morphology | FG | CTG | VI | LNM | pStage |
|---|---|---|---|---|---|---|---|
| 1 | E | none | G2 | G1 | - | | Stage I |
| 2 | T | nesting, trabecular | G3 | G2 | + | + | Stage IV |
| 3 | E | none | G2 | G1 | - | | Stage I |
| 4 | T | NE (30%), sarcomatoid (1%) | G4 | G3 | + | | Stage III |
| 5 | T | none | G2 | G1 | - | | Stage I |
| 6 | E | none | G2 | G1 | - | | Stage I |
| 7 | T | none | G2 | G1 | - | | Stage I |
| 8 | T | none | G4 | G3 | + | - | Stage III |

T, typical; E, eosinophilic; NE, neuroendocrine; FG, Fuhrman Grade; CTG, chromophobe tumor grade; VI, vascular invasion, LNM, lymph node metastasis; +, present; -, absent.

Metastasis to lymph nodes was noted in one tumor. The pathological stage consisted of five tumors in stage I, two in stage III and one in stage IV.

*Therapy, follow-up duration and outcome*

All data are summarized in Table 4. Surgical treatment was performed in all cases, which consisted of four tumors in radical nephrectomy and four in partial resection. Additionally, VEGF/PDGF inhibitor was administered for metastatic disease in two patients (cases 2 and 8). Furthermore, one patient (case 2) received mTOR inhibitor and underwent $\gamma$-knife for brain metastasis. The follow-up data was available in seven patients. The follow-up duration ranged from 21 to 108 months with a mean of 45.7 months. Four patients (cases 1, 5, 6, and 7) was alive without disease and two patients (cases 4 and 8) were alive with metastasis to lung/

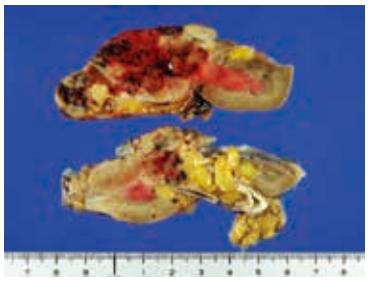
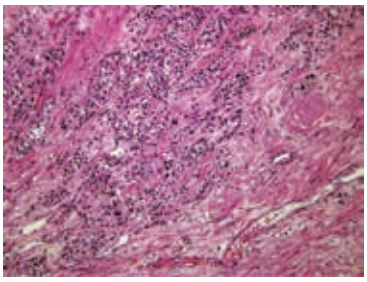


Fig.1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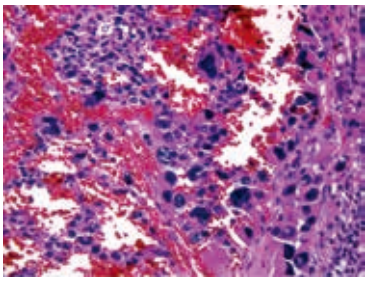


Fig.2f

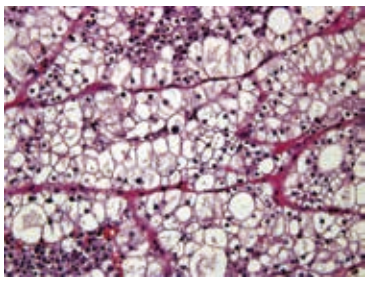
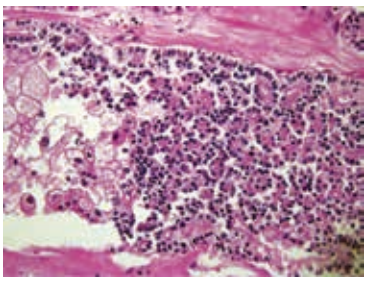


Fig.2a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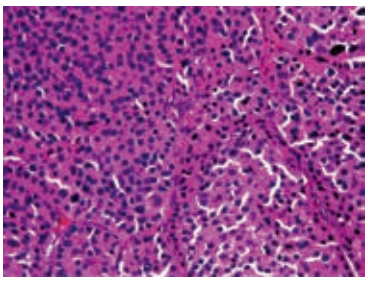
Fig.2g

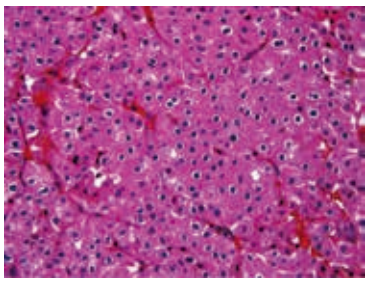
Fig.2b

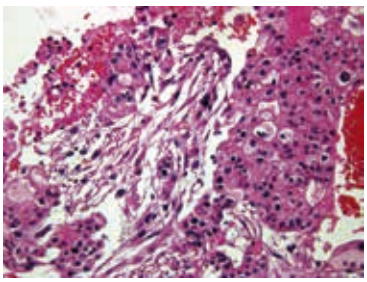
Fig.2e

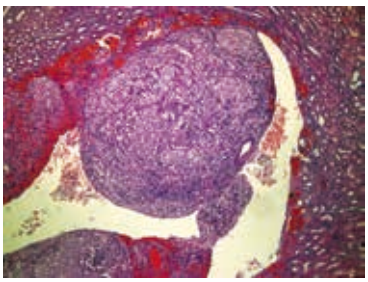
Fig.2h

FIG.1: Macroscopic finding of chromophobe RCC. Hemorrhage and necrosis are seen.
FIG.2: Microscopic finding of chromophobe RCC. (a) Typical variant. Pale cells predominately proliferate. Chromophobe Tumor Grade (CTG) 1. (b) Eosinophilic variant. Eosinophilic cells predominately proliferate. CTG 1. (c) Nesting or trabecular growth pattern is seen on the fibrotic stroma. (d) Rosette formation is observed. (e) Spindle neoplastic cells proliferate. This finding corresponds to Fuhrman Grade 4 and CTG 3. (f) Tumor cells demonstrate pleomorphism, giant cells and bizarre nuclei. This finding corresponds to Fuhrman Grade 4 and CTG 3. (g) CTG 2. Nuclear crowding is present. (h) Vascular invasion is present.

TABLE 4: Summary of therapy, follow-up duration and outcome

| Case | Surgery | Additional therapy | Follow-up duration | Clinical outcome |
|---|---|---|---|---|
| 1 | P | none | 108 months | AWOD |
| 2 | R | VEFG・PDGF-I, mTOR-I, γ -knife | 21 months | DOD |
| 3 | P | none | - | Lost |
| 4 | R | none | 52 months | AWD, Lung, LN metastasis |
| 5 | P | none | 52 months | AWOD |
| 6 | R | none | 39 months | AWOD |
| 7 | P | none | 25 months | AWOD |
| 8 | R | VEFG・PDGF-I | 23 months | AWD, Liver metastasis |

P, partial resection; R, radical nephrectomy; AWOD, alive without disease;

AWD, alive with disease: DOD, die of disease, LN, lymph node.

lymph nodes and liver, at 52 and 23 months after the operation, respectively. In patient case 8, live metastasis appeared during the follow-up period. One patient (case 2) died of disease at 21 months postoperatively.

*Comparison of Progression-free survival between chromophobe RCC and clear cell RCC*

Unexpectedly, progression-free survival of chromophobe RCC was worse than that of clear cell RCC. However, there was statistically no significant difference between two groups (Fig. 3).

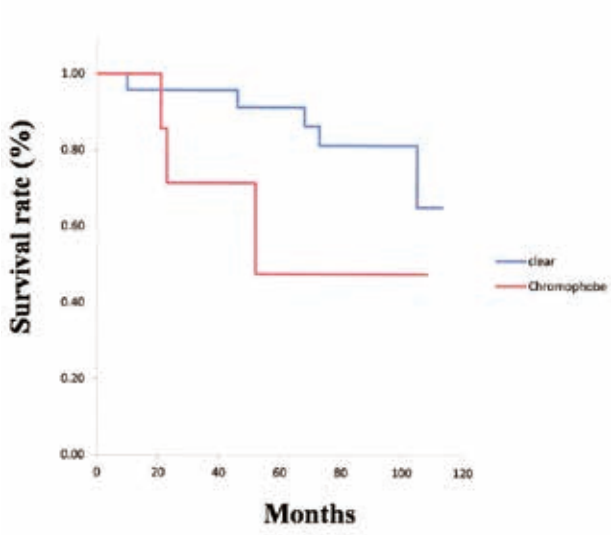


FIG. 3: Progression-free survival curve on two histologic subtypes. There was no significant difference between chromophobe and clear cell RCC groups.

## DISCUSSION

In the present study, the incidence of chromophobe RCC was 7.3% of all renal tumors. This frequency is compatible with the previous reports.[1,11] Patients with chromophobe RCC were significantly younger and tended to be more frequently female.[6,9,12] However, male patients were predominant in this study. Imaging analysis, chromophobe RCC often showed homogenous enhancement in computed tomography scan.[23] At contrast, chromophobe RCC showed heterogeneous enhancement in four tumors. This result may reflect macroscopic hemorrhage or necrosis.

The prognosis of chromophobe RCC is controversial. Some reports show better prognosis in chromophobe RCC than that in clear cell RCC[1,8,10,11,] whereas other reports demonstrate that the prognosis of these two RCC is identical.[5,6] The results in the present study support the latter hypothesis. As other prognostic indicators of chromophobe RCC, more than 8cm in tumor size, the association of papillary RCC, necrosis, vascular invasion, sarcomatoid change, CTG and pStage have been previously suggested.[3,7,10,11,20,24] In the present study, there was no case with the association of papillary RCC. However, it is possible that all factors except for the association of papillary RCC may be involved in the aggressive biological behavior in chromophobe RCC on the basis of results of this study. However, the number of cases with chromophobe RCC in the present study is too small to draw the definitive conclusion. Regarding the nuclear grade, it has been described that Fuhrman Grade is associated with the prognosis of chromophobe RCC in some reports.[3,25] However, it is widely accepted that there is no association between Fuhrman Grade and prognosis of chromophobe RCC and this idea has been incorporated into the recent ISUP grading system.[14-17] Recently, Paner et al. have proposed the

new grading system for chromophobe RCC, namely CTG.[18] They concluded that CTG is associated with the prognosis of chromophobe RCC,[18] whereas Przybycin et al. and Cheville et al. argue against this opinion.[19,20] In this study, we found that the presence of usual histological features such as neuroendocrine morphology or breast cancer-like morphology may be worse prognostic indicators of chromophobe RCC.[21,22] Neuroendocrine morphology may be related to increased density of neoplastic cells with CTG 2 and be associated with loss of chromosomes 4, 5 and 16p.[26] Oncofetal protein, IMP3, may be a useful predictor of metastasis in chromophobe RCC.[27]

Regarding the therapy of metastatic chromophobe RCC, VEGF/PDGF inhibitor or mTOR inhibitors has been tried and some cases respond to these therapies.[28-31] However, these agents seem to be usually less reactive in chromophobe RCC than clear cell RCC. Further examination in a large scale study will be required in the near future. It seems to be unlikely that immune checkpoint therapy will be available in chromophobe RCC.[32]

In conclusion, several factors such as more than 8cm in maximum diameter, macroscopic necrosis, vascular invasion, more than CTG 2 and usual histological features including neuroendocrine differentiation and mammary-like carcinoma may be worse prognostic indicators.

## ETHICAL STANDARD

This study (No.228) was approved by the ethical committee of Kochi Red Cross Hospital.

## DUSCLOSURE STATEMENT

No declared.

## FUNDINGS

The authors declare that we have no funding to disclose.

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