Original Article

Chromophobe renal cell carcinoma: Comprehensive analysis of 11 cases

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ABSTRACT

Background: Chromophobe renal cell carcinoma (chRCC) is a subtype of RCC. chRCC is diagnosed mainly in sixth decade of life. An incidence of chRCC is similar in both men and woman. Eighty-six percent of chRCCs cases are diagnosed in early stages. To analyze the clinical behavior of chRCC, we retrospectively evaluated the data from our hospital. The aim of this study was to evaluate the incidence, clinical presentation, prognosis, and clinical outcome of chRCC in a retrospective series of nephrectomy specimens. **Materials and Methods:** We retrospectively looked at our hospital database, which included 318 patients who had undergone surgery for RCC between January 2000 and December 2013. Several parameters were noted in each patient, which included age, sex, symptoms at presentation, Eastern Cooperative Oncology Group performance status, tumor diameter, tumor node metastasis stage and grade, histologic cell type, follow-up time, local recurrence, disease progression, and death. **Results:** Of 318 patients included in the database, 11 (3.45%) had chRCC. Preoperatively, 9 (81%) had T1 lesions, and the remaining 2 (18.9%) had T2 lesions. Of the T1 lesions, 6 had tumors ≤4 cm (T1a) in diameter and the remaining 3 had tumors >4 cm (T1b) in diameter. The mean survival of the patients was 99.27 ± 27 months. **Conclusions:** Our series confirms a favorable outcome for the chRCC subtype with little local aggressiveness and a low propensity for progression and death from cancer.

Key words: Chromophobe renal cell carcinoma, metastatic renal cell carcinoma, renal cell carcinoma

INTRODUCTION

Renal cell carcinoma (RCC), accounts for 2-3% of all adult malignant neoplasms and is the most lethal of all common urological cancers.[1] RCC is primarily a disease of the elderly patient, with the typical presentation in the sixth and seventh decades of life.[2,3] The majority of cases of RCC are believed to be sporadic and only 2% to 3% are familial.[4] All RCCs are, by definition, adenocarcinomas, derived from renal tubular epithelial cells.[1,2] Most RCCs share ultra-structural features, such as surface microvilli and complex intracellular junctions, with normal proximal tubular cells, and are believed to be derived from this region of the nephron.[1]

The 2004 World Health Organization classification of RCC recognized several subtypes of RCC. Most common subtypes are: Clear cell RCC (70%), papillary RCC (10-15%), chromophobe RCC (chRCC) (4-6%), collecting duct carcinoma (about 1%) and unclassified RCC (4-5%).[5,6] chRCC was first described by the ones and colleagues in 1985[1] and were a distinctive histologic subtype of RCC that appears to be derived from the cortical portion of the collecting duct.[1,7] The tumor cells typically exhibit a relatively transparent cytoplasm with a fine reticular pattern that has been described as a "plant cell" appearance. A perinuclear clearing or "halo" is typically found, and electron microscopic findings consist of numerous 150-300 nm microvesicles, which are the single most distinctive and defining feature of chromophobe cell carcinoma.[8,9] These microvesicles characteristically stain positive for Hale colloidal iron, indicating the presence of a muco-polysaccharide unique to chRCC.[10] Most chRCCs also stain positive for various cytokeratins and most are negative for vimentin.[11] Genetic analysis has revealed multiple chromosomal losses, most frequently the whole chromosomes 1, 2, 6, 10, 13, 17, and 21, and flow cytometric analysis has demonstrated hypodiploid DNA content in most cases.[12,13]

We retrospectively reviewed our series of patients with RCC and in particular chRCC. The aim of this study was

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to evaluate the incidence, clinical presentation, prognosis, and clinical outcome of chRCC in a retrospective series of nephrectomy specimens. Our study does not involve comparison of chRCC with other variants as there is not much data present.

MATERIALS AND METHODS

We retrospectively looked at our hospital database which included 318 patients who had undergone surgery for RCC between January 2000 and December 2013. The clinical charts were retrospectively reviewed. Patients with von Hippel–Lindau disease and those requiring hemodialysis were not included in this study. The pathologic stage and grade were assigned in accordance with the latest tumor node metastasis (TNM) staging.[1,2,6] Tumor size was determined from the pathologic specimens as the greatest diameter in centimeters. The Heidelberg classification was used to stratify the histologic subtypes.[1,2,5,6] The general health status was measured using the Eastern Cooperative Oncology Group (ECOG) performance status score. For statistical analysis, patients were stratified by an ECOG performance status of 0 versus 1 or more.

Several parameters were noted in each patient, which includes age, sex, symptoms at presentation, ECOG performance status, tumor diameter, TNM stage and grade, histologic cell type, follow-up time, local recurrence, disease progression, and death. At the most recent follow-up visit, the vital status was evaluated and described as alive (no evidence of disease or disease progression), deceased (by disease, of any other cause with or without evidence of disease, and by any treatment complication).

The patient presentation was categorized as incidental or symptomatic. All patients underwent preoperative computed tomography scan of the kidney ureter and bladder region and chest X-ray. During the follow-up period, the patients underwent a physical examination, routine laboratory evaluation, and imaging studies every 6 months for the 1st year and yearly thereafter. Data from patients lost to follow-up were actualized by contacting relatives. The survival rates were determined using the Kaplan–Meier method and were calculated using the date of surgery to the date of death or last follow-up.

RESULTS

Of 318 patients included in the database, 11 (3.45%) had chRCC 4 (36.36%) were men and 7 (63.63%) women. The mean patient age was 59.36 ± 6.65 years (range: 54-76). The tumor was located in the right kidney in six patients (54.5%) and in the left kidney in 5 (45.5%), no familial or bilateral disease was observed. None of the tumors showed multifocality.

Of the 11 patients, 8 (72.7%) were asymptomatic at diagnosis, 3 (27.3%) presented with local symptoms related to a renal mass (hematuria, pain), and 2 (18.18%) complained preoperatively of systemic symptoms (fever, generalized weakness). The asymptomatic tumors were detected by abdominal ultrasonography or computed tomography. At the time of presentation, all patients had ECOG performance status of 0. Preoperatively 9 (81%) had T1 lesions, and the remaining 2 (18.9%) had T2 lesions. Of the T1 lesions, 6 had tumors ≤4 cm (T1a) in diameter and the remaining 3 had tumors >4 cm (T1b) in diameter. All patients[6] with incidentally diagnosed T1a lesions underwent partial nephrectomy whereas the remaining five underwent radical nephrectomy. Histopathological examination confirmed the chromophobe variety of RCC. The microscopic features were classical. Resected lymph nodes did not show evidence of metastasis in any of the patients. Surgical margins were clear. None of the patients had any major intra/postoperative complications.

The mean follow-up of the patients is months. During this period, none of the patients had local recurrence of the disease, whereas the two patients (18%) with T2 disease developed distant metastases, one in the chest and the other in bony pelvis and left femur. Both these patients died 12-15 months following diagnosis of the metastases. Both the patients did not receive any further treatment for metastasis as the patients/attenders could not afford treatment with sumitinit/sucfinit/pazopanile. One other patient who neither had local recurrence or distant metastases died due to noncancer cause [Figure 1]. The mean survival of the patients was 99.27 ± 27 months. All the eight patients surviving to date (December 2013) have ECOG performance status of 0.

DISCUSSION

Renal cell carcinoma is a heterogeneous disease, comprised of different histological variants with distinct clinical

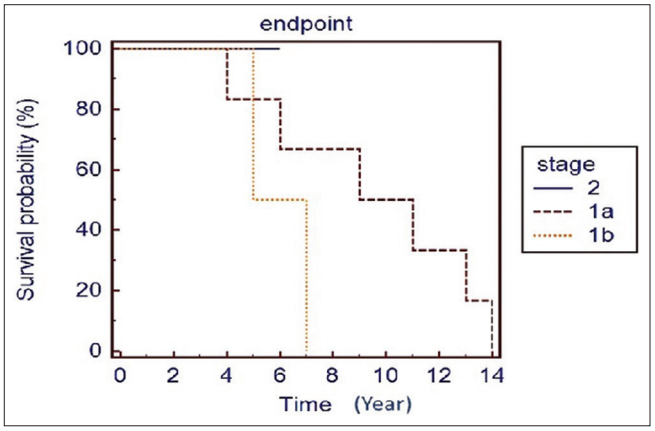

Figure 1: The graph showing the survival probability of patients alive and death

course, genetic changes and response to systemic treatment. chRCC comprise 5% of all the cases of RCC. The mean age of occurrence is in the fifth decade, with a range of 27-86 years, more commonly observed in women (52%) than in men (48%).[14] chRCC are usually located in the renal cortex. Presence of cystic areas as well as multifocality (10% to 12%) is usually rare.[14] Most of the cases present early and are diagnosed to have either stage I or II lesions. Renal vein invasion is seen in 5% of cases and incidence of metastatic disease is 6-7%. The most common sites of metastases are liver (39%) and lung (36%).[14]

Macroscopically, chRCC are well-circumscribed highly lobulated solid neoplasms. Microscopic features are [Figure 2a and b] that of a solid tumor, at times tubulocystic, with broad fibrotic septa. In general two different types of tumor cells are present in varying proportions. The first type includes pale polygonal cells with abundant transparent cytoplasm and prominent cell membranes.[14,15] These cells are admixed with a second population of smaller cells with granular and eosinophilic cytoplasm. The nuclei of both appear irregular. Binucleation and perinuclear halos are commonly seen.[14,16] There are different variants of chRCC according to the proportion of cells. The eosinophilic variant (>80% eosinophilic cells) shares certain characteristics with oncocytomas (nested, alveolar or sheet like architecture with eosinophilic granularity, perinuclear clearing and peripheral accentuation of cytoplasm). This type is often bilateral (11%) and multifocal (22%). The classic type (>80% pale cells) is associated with necrosis and sarcomatoid changes (aggressive tumors with a high potential for distant metastases). Mixed chRCC have variable architecture.[17]

Birt–Hogg–Dube syndrome is an autosomal dominant condition characterized by a familial tendency to develop multiple cutaneous fibrofolliculomas and trichodiscomas of the hair follicle.[1,18] Several studies have reported a predisposition for these families to develop multifocal or bilateral renal cancer, particularly chRCC.[1,18-20]

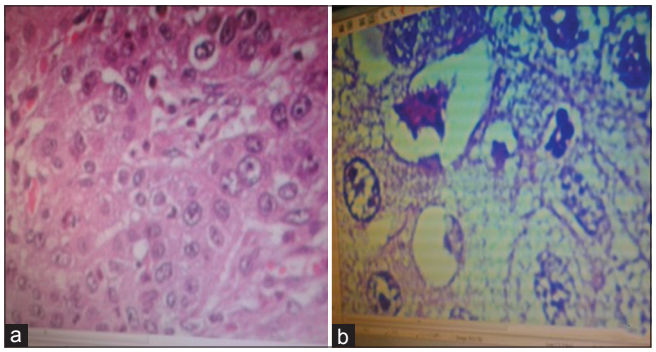

Figure 2: (a) H and E, ×10 image-shows mixture of classic (chromophobic) and eosinophilic cells, with distinct cytoplasmic borders, perinuclear halos, and nuclear "raisins." (b) ×40 chromophobe renal cell carcinoma stains positive for Hale colloidal iron and demonstrate multiple microvesicles

Cindolo *et al*.[21] retrospectively analyzed the clinical behavior of chRCC, from a database of 3228 patients who underwent surgery between 1986 and 2002 in six European centers. Of the 3228 patients, 104 (3.2%) affected by chRCC were identified. The mean age at diagnosis was 57.6 years (range: 22-83). Of the 104 patients, 51 (49%) were men, and 53 (51%) were women. The mean tumor size was 6.4 ± 3.6 cm. An incidental diagnosis accounted for 61.5% of the cases. Radical nephrectomy was performed in 88 patients (85%). After a median follow-up of 38 months (mean 44, range: 1-153), no local recurrence was observed. The 5 years overall survival rate for chRCC was 81%. Of the 104 patients, 5 (4.8%) and 9 (8.6%) died of unrelated causes and renal cancer, respectively. However, the authors did not find any incidence of familial or inherited tumor.

Przybycin *et al*.[22] studied 203 consecutive primary chRCCs resected at their institution. Over median follow-up of 6.1 years (range: 0.1-18 years), 5 years and 10 years disease specific events occurred in 3.7% (95% confidence interval [CI]: 1.5%, 7.4%) and 6.4% (95% CI: 2.7%, 12.2%) patients. Outcomes showed a significant association with tumor size, small vessel invasion, sarcomatoid features and microscopic necrosis ($P \leq 0.05$ each). On the basis of their long-term follow-up the authors concluded that chromophobes seemed to have better clinical outcomes than those reported for clear cell and papillary RCCs.

In 1995, Akhtar *et al*.[23] reported that 19% of the chRCCs were incidentally diagnosed. By contrast, Peyromaure *et al*.[24] recently described 68.8% rate of incidental chRCC. In our series, 64% of the patients had no symptoms related to a kidney tumor at diagnosis. This finding could be explained by the large proportion of patients with low-stage tumors and the widespread use of noninvasive imaging techniques. In our series to the incidence of incidentally diagnosed chRCC was %. Several recent reports have confirmed good prognosis as well as survival rates in patients with chRCC. Cheville *et al*.[6] and Beck *et al*.[25] showed that the 5 years cancer-free survival rate was 86.7% and the disease-free survival rate was 80.1%. Cindolo *et al*.[21] reported a 3 years and 5 years overall survival rate for chRCC of 94% and 81%, respectively (mean follow-up 44.2 months). Compared with other variants of RCC, chRCC showed a better prognosis (at last follow-up, 91.3% of the patients were alive without evidence of disease) with very low rates of progression and cancer-related death. The cancer-related death rate was 22%, 16%, and 8.6% for clear, papillary, and chRCC in their series with the same follow-up. This was because more than 70% of patients had organ-confined disease (stage T2 or less) and more than 60% of tumors were well or moderately differentiated. Moch *et al*.[26] and Cheville *et al*.[6] considered the percentage of histologic tumor necrosis also of prognostic value.

In our series too patients with chRCC presented with low-grade and low-stage disease and there was disease progression seen in only 18%. None of the patients exhibited bilateral disease, nor any patients had metastatic disease at presentation.

CONCLUSIONS

Our study confirms a general favorable outcome for chRCCs, which are predominantly low-stage and low-grade tumors. These tumors had little local aggressiveness, as well as a low propensity for progression and death from cancer. Metastasis at diagnosis and disease progression after nephrectomy is rare. A radical surgical approach remains the reference standard therapy, but nephron-sparing techniques are also associated with good outcome, especially for those patients with a well-documented resectable mass.

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