**Review paper**

**Review of hereditary leiomyomatosis renal cell carcinoma with focus on clinical and pathobiological aspects of renal tumors**

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The entity of hereditary leiomyomatosis renal cell carcinoma (HLRCC)-associated RCC has been proposed and integrated into the recent International Society of Urologic Pathology (ISUP) of renal tumors. This tumor is characterized by presence of cutaneous and/or uterine leiomyomas and RCC and autosomal dominant hereditary form. Grossly, HLRCC arising in the kidney show the solid tumor with frequent partial cystic area. Microscopically, the tumor typically shows papillary RCC, type 2, with eosinophilic large nucleoli reminiscent of cytomegalovirus viral inclusion and perinuclear clear haloes.

**Key words:** Hereditary leiomyomatosis renal cell carcinoma, pathology, review.

**Introduction and history**

Kloetzer et al. for the first time described a hereditary form of multiple cutaneous leiomyoma (MCL) [1]. Reed et al. reported a hereditary syndrome of cutaneous leiomyomas and uterine leiomyomas and/or leiomyosarcoma inherited in an autosomal dominant fashion [2]. After then, this disease was designated as Reed syndrome. In 2001, Launonen et al. and Kiaru et al. suggested that RCC with papillary architecture can occur in patients with Reed syndrome and this syndrome was designated as hereditary leiomyomatosis renal cell carcinoma (HLRCC). They found that MCL, Reed syndrome and HLRCC are single disease with a variable phenotype [3, 4]. Additionally, Launonen et al. found that the responsible gene for HLRCC is mapped to chromosome 1q42.3-q43 [5]. In 2002, Tomlinson identified that germline mutations of FH gene mapped to this chromosome in HLRCC neoplasms [5]. Of HLRCC patients, in 2013, HLRCC-associated renal tumors has been incorporated into the classification of renal tumors in International Society of Urologic Pathology (ISUP) [6]. In this article, we review HLRCC with focus on clinical and pathobiological aspects of renal tumors.

**Definition/diagnostic criteria of the disease entity**

The major criteria (high likelihood of HLRCC) is multiple cutaneous piloleiomyomas with at least biopsy proven and histologically confirmed. The minor criterion (suspicous for HLRCC) contains three items. One is multiple symptomatic uterine leiomyomas before age 40. The other is papillary RCC, type 2 in early onset before age 40. The remaining one is family history of HLRCC plus solitary cutaneous leiomyoma or at-first-degree family member who meets one of the above-described criteria. The diagnosis of HLRCC is likely when a proband meets the major criterion and may be suspected when a proband meets at least two minor criteria [7, 8]. For the definitive diagnosis, positive results of germline FH-mutation analysis will be required [8].

**Epidemiology**

Although the majority of HLRCC female patients is associated with cutaneous and/or uterine leiomyomas [9], only a minority (15-35%) of HLRCC develop RCC [10, 11, 12, 13, 14]. There is no sex predominance [13, 15]. According to the study of Wong et al., the difference in age at the diagnosis of RCC between the first and second generation, and between the first and third generation are –18.6 and –36.2 years, respectively. These results suggest that RCC tend to occur at the younger age in persons with family history of HLRCC renal cancer in their father/mother or grandfather/grandmother [17]. About 7% of HLRCC patients are diagnosed with RCC before 20 years [15, 18, 19, 20]. The risk of RCC in patients with HLRCC is higher with 6.5 fold than that of general populations [21]. Renal cysts are found in 42% of FH gene mutation-positive patients [10, 21, 22, 23, 24, 25].

**Clinical symptoms**

Patients with HLRCC renal tumors present with hematuria, abdominal/flank mass, abdominal/flank pain, abdominal discomfort, fatigue or weight loss [16, 25, 26, 27, 28]. Rare cases may be incidentally found [16].

**Other clinical features**

The association of male infertility, adenocortical hyperplasia/tumor, thyroid follicular carcinoma, cutaneous basal cell carcinoma, bladder cancer, liver hemangiomia, Leydig cell tumor, ovarian cystadenoma, gastrointestinal stromal tumor, breast cancer, leukemia, cutis verticis gyrata, eruptive collagenoma and Charcot-Marie-Tooth disease has been previously reported [3, 7, 21, 28, 29, 30, 31, 32, 33].

**Imaging findings**

Abdominal computed tomography (CT) scan show the hypodensity lesion in the kidney [9, 20, 26]. The contrast enhanced CT shows homogenous or inhomogenous and less enhanced mass [18, 34, 35, 36].

**Pathological findings**

**Macroscopic findings**

Grossly, most tumors were solid, but half of tumors show the cystic area partially [15]. The size of the tumor ranges from 2.3 to 20 cm [15]. There is no predilection in laterality [15, 16]. The tumors frequently invade capsule and autophagic adipose tissue as well as renal vein and vena cava [15, 16]. HLRCC renal tumors generally present as solitary and unilateral lesion, but some tumors can occur multifocally or bilaterally [8, 15, 16, 17, 37, 38, 39].

**Microscopic findings**

Microscopically, the tumor is composed of neoplastic cells with various morphological architectures such as papillary, tubulopapillary, solid, cystic tubulocystic, vacuolated/cystiform or mixed patterns [8, 15, 16, 22, 40]. Regarding the histological subtype, papillary RCC, type 2 is most frequent, but collecting duct carcinoma may be seen [3, 7, 9, 11, 17, 18, 22, 35, 36, 37, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50]. Clear cell RCC, unclassified RCC, oncocytic tumor, cystic tumor, angiomylipoma or Wilms tumor has been described [7, 37, 39, 49, 50, 51, 52, 53]. The most important hallmark of HLRCC renal cancer is prominent eosinophilic nucleoli and perinuclear clearing/haloes resembling cytomegaloviral inclusion [15, 13, 16, 25, 27, 34, 40]. Rhabdoid features or multifocalated tumor giant cells may be noted [25]. Fuhrman nuclear grade generally correspond to grade 3 or 4 [17]. Renal cysts or tubular cells with hob-
nail patterns in the renal parenchyma adjacent to the main tumor may be present [10]. Renal cyst can occur solitarily or multifocally [22, 24, 25]. Renal tumor can develop independently or within renal cysts [22].

Immunohistochemical findings

The application of S-(2-succino)-cysteine (2SC) may be useful for the detection for HLRCC renal tumors, but primary antibody against 2SC is not commercially available [16]. Regarding 2SC staining pattern, both cytoplasmic and nuclear staining is significant for the accurate detection of HLRCC renal tumors, but primary antibody against 2SC is not commercially available [16]. Regarding 2SC staining pattern, both cytoplasmic and nuclear staining is significant for the accurate detection of HLRCC renal tumors, but primary antibody against 2SC is not commercially available [16].

Differential diagnosis

Pathologists should differentiate HLRCC renal tumors from papillary RCC, type 2, collecting duct carcinoma (CDC), clear cell RCC, tubulocystic carcinoma, macronodular tubular and spindle cell carcinoma (MTSCC), Xp11.2 RCC, ALK renal cancer and renal oncocytoma. Among them, the distinction from papillary RCC and CDC is most important. The presence of prominent eosinophilic nuclei and perinuclear halos may be diagnostic clue to HLRCC renal tumors [13, 15, 16, 25, 27, 34, 40]. However, the association of cutaneous or uterine leiomyomas are the presence of family history of cutaneous and/or uterine leiomyomas, particularly occurring at the young age, or renal tumors are more prone to develop in families with suggestive clinical features [5, 7, 9, 11, 21, 22, 35, 36, 41, 44, 47, 49]. LOH at FH gene locus is observed in 80% of HLRCC renal tumors [3, 15, 37, 42]. Pathological features may suggest the possibility of MTSCC. The break part fluorescence in situ hybridization for TFE3 and ALK gene leads to the final diagnosis of Xp11.2 RCC and ALK renal cancer, respectively.

Characteristics of cutaneous leiomyoma

The tumors are usually multiple and the size of the tumor generally ranges from 0.2 to 2.0cm [1, 7, 61, 62]. The tumor present as papules and/or nodules in groups, dermal or linear arrangement, and range from flesh, erythematous to pink-brown in color [1, 7, 61, 62, 64, 65, 66]. The location of the tumor involves extremities, shoulders and trunk, but face or neck can be distributed [1, 7, 8, 61, 62, 63, 64, 65, 66]. With the age, the lesions tend to increase in size and number [7, 62]. Most patients present with pain or itching in response to touching or temperature [7, 8, 62]. Histologically, the tumor display the form of piloleiomyoma, but cytologic atypia is generally absent [1, 7, 61, 62, 63, 64, 65, 66]. Rarely, the occurrence of leiomyosarcoma has been described [9].

Characteristics of uterine leiomyoma

The risk that women with HLRCC develop uterine leiomyomas is higher in 8–9 to 71 fold than that of general population [21, 67]. The mean age of HLRCC patients at diagnosis of uterine leiomyoma is 28 years, namely 10 years younger than the general population and surgical resection is frequently carried out on women before 30 years of age because of severe symptoms such as abdominal pain, menorrhagia and metorrhagia [7, 8, 14, 55, 57, 58, 59]. Tumors generally occur in a multiple form, and occurrence at the younger age and more than seven tumors in number may be speculated as HLRCC uterine leiomyomas [55, 57, 58, 59]. Uterine leiomyoma with patients with HLRCC have characteristic of cellular morphology, prominent eosinophilic nuclei, perinuclear haloes, cytoplasmic eosinophilic globules [56, 57, 59]. Atypia, multinucleated giant cells, fibriillary cytoplasm, epithelioid growth pattern, schwannoma-like growth pattern, “Orphan Annie nuclei” with optical clearing, and hemangioepitheliomatous blood vessels can be observed [56, 57, 59, 68]. In some cases, leiomyoma may progress to leiomyosarcoma [57]. Immunohistochemically, tumor cells are positive for 2SC [59, 67].

Molecular genetic findings

Biallelic inactivation of FHI gene occurs in renal tumors of HLRCC patients [3, 9, 16]. In most tumors, germline inactivation occurs in one allele and loss of heterozygosity (LOH) at FHI gene locus or somatic mutation of FHI gene in the other allele [5, 9, 16]. Pathogenic germline mutation of FHI gene have been detected in 61% of families with suggestive clinicopatho-

Phenotype-genotype correlation

There seems to be no relationship between pheno-
type and genotype in HLRCC to date [9, 69]. There is no evidence of a genetic modifier for RCC risk in HLRCC [77]. The environmental factor may modify the development of RCC [78].

Prognosis

HLRCC renal cancer, particularly papillary RCC, type 2 and CDC behave in an aggressive fashion and most cases generally die of disease within 5 years since the initial diagnosis [8, 11, 13, 15, 16, 17, 18, 20, 25, 27, 28, 35, 38, 41, 45, 46, 47, 48, 49, 50, 62, 64, 75, 76]. Approximately two thirds of patients show stage III/IV at the diagnosis [7]. Seventy-four percent of patients with HLRCC renal cancer die of metastatic disease [44, 79]. The most frequent metastatic site is regional lymph node, but the metastasis to distant lymph node can occur [15, 16, 35, 36]. Furthermore, distant metastasis to lung, bone and liver has been reported [15, 16, 35, 36, 48]. Dissemina-
tion to peritoneum, pleura and meninges can occur [15, 25, 48].

Therapy

When the solid renal tumor at the early stage is dis-
covered, surgical resection with wide resection mar-
gin including radical nephrectomy and retroperito-
nal lymph node resection is necessary. Because of frequent lymph node metastasis should be promptly performed [45, 80, 81]. Radiofrequency or cryoablation should not be recommended [8]. The patients with advanced disease may benefit from molecular targeted therapy such as multikinase inhibitor (sunitinib, sorafenib and pazopanib) including immunotherapy such as Interferon or Interleukin-2, neoadjuvant therapy and chemotherapies for metastatic sites [48]. However, these therapies seem to be not so effective for advanced tumors.

Clinical management

Active surveillance is not recommended for HLRCC renal tumors [80, 81]. The FH gene mu-
tation analysis and annual surveillance should start at the age of 8 to 10 years or even as early as 5 years [7, 8, 17, 19, 79]. FH gene mutation carriers should identify in three of analyzed eleven HLRCC renal tumors with papillary type 2 morphology using array comparative genomic hybridization [76].
them, somatic mutation of FH gene was identified in one bladder cancer and three breast cancers. Therefore, these disease may be a part of HLRCC syndrome [21]. However, Kistler et al. confirmed that FH gene is not a major predisposing gene for familial breast cancer [82]. Further examinations in a large scale study will be needed in order to elucidate the relationship between FHLC, and bladder/breast cancer or other associated lesions. As the HLRCC renal cancer generally gives rise to a dismal outcome, the early detection/treatment is very important for the management of patients with HLRCC. From this point of view, the extensive research on precursor lesion such as lobular tubular cells or associated renal cysts may be key target. Regarding the management of renal tumors from the family members, the complication of the HLRCC renal tumors will be needed in the future.

The authors declare no conflicts of interest.

References

31. Oberrauch JM, Wormalt D, Heyman K, et al. A clinical approach to the management of renal tumors from the family members, the complication of the HLRCC renal tumors will be needed in the future.


