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 cytomegaloviral inclusion and perinuclear clearing/haloes. Immunohistochemically, tumor cells show the overexpression for 2SC and reduced expression of FH. Germline mutation of *fumarate hydratase (FH)* gene, the HLRCC responsible gene mapped to chromosome 1q43, has been identified in patients with HLRCC. As the renal cancer in patients with HLRCC generally behave aggressively even in a small size, complete surgical resection and retroperitoneal lymph node resection should be performed promptly when the tumor is discovered. The surveillance of renal tumor in *FH* gene germline mutation-positive patients should be started from the early age using ultrasound sonography or magnetic resonance imaging.

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

Introduction and history

Kloepfer *et al*. for the first time described a hereditary form of multiple cutaneous leiomyomata (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 Kiuru *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 cancer (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 [3]. In 2002, Tomlinson identified that germline mutation 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 (suspicious 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 [15, 16]. 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, adrenocortical hyperplasia/tumor, thyroid follicular carcinoma, cutaneous basal cell carcinoma, bladder cancer, liver hemangioma, Leydig cell tumor, ovarian cystadenoma, gastrointestinal stromal tumor, breast cancer, leukemia, cutis verticis gyrate, 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 capsular and perinephric 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/cribriform or mixed pattern [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, angiomyolipoma 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 perinucleolar clearing/haloes resembling cytomegaloviral inclusion [13, 15, 16, 25, 27, 34, 40]. Rhabdoid features or multinucleated 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-

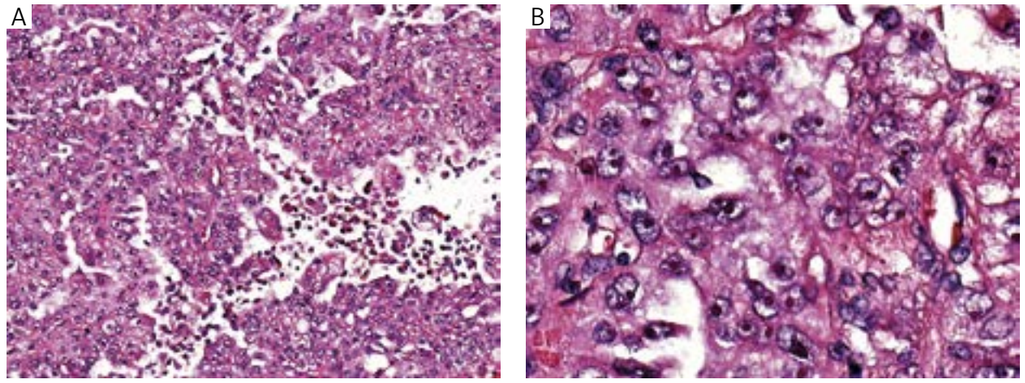

Fig. 1. Microscopic findings. (A) The typical HLRCC renal tumor consists of neoplastic cells with papillary configuration and eosinophilic cytoplasm. (B) High magnification. Neoplastic cells have large eosinophilic inclusion-like nucleoli and perinuclear haloes

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 some sporadic type renal tumors may show the only cytoplasmic positivity for 2SC [16]. The tubular cells with hobnail pattern adjacent to the dominant tumor showed the positive reaction for 2SC. This finding suggests that hobnail tubular cells may be precursor lesions of HLRCC renal tumors [25, 39]. Except for 2SC, there is no characteristic marker of HLRCC [15]. The positivity for PAX8, CD10, vimentin, cytokeratin 8/18, HIF-1a and GLUT1 has been reported [25, 54]. The increased nuclear accumulation of p53 protein has been described [25]. The Ki-67 index is high [35]. TFE3 is negative [15].

Differential diagnosis

Pathologists should differentiate HLRCC renal tumors from papillary RCC, type 2, collecting duct carcinoma (CDC), clear cell RCC, tubulocystic carcinoma, mucinous 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 nucleoli and perinucleolar halo 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 vital diagnostic clues for the identification of HLRCC [55, 56, 57, 58, 59]. Tubulocystic carcinoma with high grade carcinoma foci may be indistinguishable from HLRCC renal tumors. In this setting, *FH* gene germline mutation testing is an accurate diagnostic tool [60]. The abundant mucin deposition on the background stroma and the presence of elongated/anastomosing tubules 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, dermatomal or linear arrangement, and range from flesh, erythematous to pink-brown in color [1, 7, 61, 62, 63, 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 metrorrhagia [7, 8, 14, 55, 57, 58, 59]. Tumors generally occur in a multiple form, and occurrence at the younger age and more than seven tumor 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 nucleoli, perinucleolar haloes, cytoplasmic eosinophilic globules [56, 57, 59]. Atypia, multinucleated giant cells, fibrillary cytoplasm, epithelioid growth pattern, schwannoma-like growth pattern, "Orphan Annie nuclei" with optical clearing, and hemangiopericytomatous 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 *FH* gene occurs in renal tumors of HLRCC patients [5, 9, 16]. In most tumors, germline mutation occurs in one allele and loss of heterozygosity (LOH) at *FH* gene locus or somatic mutation of *FH* gene in the other allele [5, 9, 16]. Pathogenic germline mutation of *FH* gene have been detected in 76-100% of 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 cancer [3, 15, 37, 42]. Epigenetic alteration seems to be rare. Germline mutations consists of missense (57%), nonsense & frameshift (27%), large deletion (4%) including whole gene deletion, small deletion (4%), duplication (2%), splice-site (6%) alterations [5, 9, 44, 69, 70, 71]. HLRCC-associated mutation occur in the 5' of the gene, whereas *FH*-deficiency mutations, autosomal recessive hereditary form with neurological impairment, tend to occur in the 3' end [41, 69, 71, 72]. Biallelic inactivation (somatic mutation plus LOH) of *FH* gene occurs in nonsyndromic uterine leiomyomas but is rare in other tumors [73]. Sporadic uterine leiomyosarcoma and cutaneous leiomyoma may show germline mutation rarely [74].

Chromosomal changes

The loss of chromosome 1q was observed as expected findings compatible with tumor suppressor role of *FH* gene [5, 8, 15, 22, 42, 75]. Additionally, gains in chromosomes 2, 7 and 17 and losses in chromosomes 13q12.3-q21.1, 14, 18 and X were identified in three of analyzed eleven HLRCC renal tumors with papillary type 2 morphology using array comparative genomic hybridization [76].

Phenotype-genotype correlation

There seems to be no relationship between phenotype 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]. Dissemination to peritoneum, pleura and meninges can occur [15, 25, 48].

Therapy

When the solid renal tumor at the early stage is discovered, surgical resection with wide resection margin including radical nephrectomy and retroperitoneal lymph node resection because of frequent lymph node metastasis should be promptly performed [45, 80, 81]. Radiofrequency or cryoablation should be not recommended [8]. The patients with advanced stage HLRCC renal tumors have previously received immunotherapy such as Interferon or Interleukin-2, molecular targeted therapy such as multikinase inhibitor (sunitinib, sorafenib and pazopanib) including VEGF pathway antagonist (bevacizumab), mTOR inhibitor (everolimus and temsirolimus) and chemotherapy (cisplatin and gemcitabine) [8, 18, 20, 36, 48, 56]. Radiation therapy has also been performed 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 solid renal tumor [80, 81]. The *FH* gene mutation 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

be examined using MRI with 1 to 3mm slice [79]. Ultrasound sonography for the kidney cannot detect small tumors because of the low sensitivity. However, as MRI might be distressing in childhood, the surveillance in childhood can be replaces by ultrasound sonography every six months by expert radiologists [7, 20]. Because of the small risk of RCC in HLRCC patients, other researchers recommend that *FH* gene analysis and surveillance should start at the age of 18 to 20 years [20, 77].

Future perspectives

The association of some diseases except for cutaneous and/or uterine leiomyomas in HLRCC has been reported [3, 7, 21, 28, 29, 30, 31, 32, 33]. Among them, somatic mutation of *FH* gene was identified in one bladder cancer and three breast carcinoma. Therefore, these disease may be a part of HLRCC syndrome [21]. However, Kiuru *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 HLRCC and bladder/breast carcinoma 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 hobnail tubular cells or associated renal cysts may be key target. Regarding the management of HLRCC family, further examination by the accumulation of the HLRCC renal tumors will be needed in the future.

The authors declare no conflicts of interest.

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