Review of renal tumors associated with Birt-Hogg-Dubé syndrome with focus on clinical and pathobiological aspects

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Birt-Hogg-Dubé syndrome (BHDS) is an autosomal dominant inherited disorder characterized by clinical features of skin lesions, pulmonary lesions and renal tumor. The gene responsible for this syndrome is located on chromosome 17p11.2 and designated as *FLCN*. In this article, we review renal tumors associated with BHDS with a focus on clinical and pathobiological aspects. Renal tumors often occur multifocally or bilaterally in the imaging analyses or gross examination. Histological examination of renal tumors includes a variety of subtypes such as hybrid oncocytic tumor, chromophobe renal cell carcinoma (RCC), oncocytoma, clear cell RCC and papillary RCC. The histologic discordance in multiple tumors seems to be characteristic of this syndrome. Oncocytosis is observed histologically in about half of the cases. Several investigations have elucidated that folliculin may be involved in the mammalian target of rapamycin (mTOR) pathway recently. Renal tumors composed of clear cells may behave in an aggressive fashion. However, renal tumors including hybrid oncocytic tumor, chromophobe RCC and oncocytoma behave mostly in an indolent fashion.

Key words: review, renal tumor, Birt-Hogg-Dubé syndrome.

Introduction and history

Birt, Hogg and Dubé reported several members of kin with thyroid cancer and fibrofolliculoma occurring in an inherited autosomal dominant fashion [1]. This syndrome was later designated as Birt-Hogg-Dubé syndrome (BHDS). However, two years earlier, Hornstein and Knickenberg described a distinct entity in two siblings with multiple perifollicular fibromas, multiple acrochordons and intestinal polyps [2]. Their father had bilateral renal cysts and bilateral lung cysts. The authors suggested that this disorder is probably based on a genetic trait. The disease has been named as Hornstein-Knickenberg syndrome. Nowadays, some investigators consider that these two syndromes are the same entity [3-6]. Accordingly, Happle proposes that this syndrome should be renamed as Hornstein-Birt-Hogg-Dubé syndrome [6].

The association of renal tumors in BHDS was first described in 1993 [7]. In this article, we present an overview of renal tumors associated with BHDS with a focus on clinical and pathobiological aspects.

Definition of the entity

BHDS is an autosomal dominant disorder characterized by the association of lesions affecting three different systems: skin lesions such as fibrofolliculoma, trichodiscoma and acrochordon; pulmonary lesions including cysts and spontaneous pneumothorax; and renal tumors [1, 2, 8-11]. The diagnostic criteria are as follows: Major criteria, 1) At least five fibrofolliculomas or trichodiscomas, at least one of them confirmed histologically, occurring in adult onset, 2) Pathogenic *FLCN* germline mutation; Minor criteria, 1) Multiple lung cysts, bilateral basally located lung cysts with no other apparent cause, with or without spontaneous primary pneumothorax, 2) Renal cancer, early onset (< 50 years) or multifocal or bilateral renal cancer, or renal tumor composed of mixed chromophobe and oncocytic morphology, 3) A first-degree relative with BHDS. When patients fulfill one major or two minor criteria, the diagnosis of BHDS is feasible [12].

Epidemiology

BHDS occurs in approximately 1/200,000 people [13, 14]. Renal tumors associated with BHDS are diagnosed at the age ranging from 20 to 75 years, but often occur before 50 years of age [3, 5, 15-17]. Renal tumors occur in 25-35% of patients with BHDS [14, 18]. There is a male predominance in renal tumors associated with BHDS [18]. The estimated penetrance of renal cancer in *FLCN* gene mutation carriers in BHDS families is 16% at 70 years of age [17]. The risk of developing renal tumors in BHDS-affected patients is approximately 7 times higher than in non-BHDS-affected patients [19]. Skin lesions arising in face, neck and anterior trunk regions are observed in approximately 80% of patients with BHDS [14]. Pulmonary cyst and spontaneous pneumothorax are identified in over 80% and nearly 25% of BHDS-affected patients [14]. The risk of developing spontaneous pneumothorax in BHDS-affected patients is approximately 50 times higher than in non-BHDS-affected patients [19].

Other clinical features

The association of parotid gland oncocytoma, thyroid carcinoma, prostatic carcinoma, breast fibroadenomatosis, breast sarcoma, jaw cancer, and colon carcinoma has been repeatedly described [16, 19-21]. Regarding skin/soft tissue lesions, focal cutaneous mucinosis, trichoblastomas, basal cell carcinomas, angiolipomas, lipomas, collagenomas, connective tissue nevi, malignant melanomas, oral papules and perivascular fibromas may be observed in BHDS [20, 22-24]. Aplasia of the internal carotid artery and flecked chorioretinopathy were also reported [20]. However, whether these diseases are really related to BHDS remains unknown.

Imaging findings

Ultrasound sonography or computed tomography scan of the kidney usually shows unilateral and bilateral solid lesions [3, 25-27]. Preoperative imaging disclosed 5.3 tumors per BHDS patients on average [18, 28]. The lesions are usually multifocal [25]. Renal cysts may be seen [29].

Pathological findings

Macroscopic findings

The tumors usually form a well-demarcated, unencapsulated mass and the cut surface shows homogeneous tan to brown color [30, 31]. Necrosis is not frequent. However, a central scar may be seen [32].

Microscopic findings

A variety of histological subtypes including hybrid oncocytic tumor, chromophobe RCC, oncocytoma, papillary RCC and clear cell RCC have been observed [9, 17, 19, 20, 22, 30, 33-35]. Hybrid oncocytic tumors have both areas reminiscent of chromophobe RCC having a well-defined cell border, pyknotic nuclei and perinuclear halo and oncocytoma showing ill-defined cell borders, finely granular eosinophilic cytoplasm and round nuclei [18] (Fig. 1A). In some hybrid oncocytic tumors, clear cells may be focally seen [8, 30] (Fig. 1B). Papillary RCC with oncocytic change, clear cell RCC with focal papillary structures, RCC with a mixture of eosinophilic and focal clear cells with tubulopapillary architecture, sarcomatoid RCC and unclassified RCC have been described [17, 29, 31, 36, 37]. The association with renal angiomyolipoma has also been reported [38, 39]. Discordance of histological subtypes is observed in 80% of bilateral/multiple renal tumors associated with BHDS [5, 40]. Renal cysts are also usually seen [41, 42]. Multifocal renal oncocytosis is observed in the surrounding grossly normal renal parenchyma in 50 to 58% of patients [43, 44] (Fig. 1C). Renal oncocytosis is characterized by a spectrum of oncocytic changes that diffusely involve the kidney parenchyma and may include a dominant oncocytic neoplasm, smaller oncocytic nodules, infiltrative appearing oncocytic cells, cortical cysts lined with oncocytic cells, and oncocytic change in non-neoplastic tubules [45]. Recently, we

found a characteristic feature of renal tumors associated with BHDS, i.e. small papillary tufts that are frequently observed in the peripheral area of the tumors (Fig. 1D).

Cytological findings

Fine needle aspiration cytology showed sheets of oncocytic cells with scattered, slightly larger, clear cells [46].

Molecular genetic findings

The *FLCN* gene is mapped to chromosome 17p11.2 and it is suggested that this gene acts as a tumor suppressor gene because *FLCN* gene mRNA is expressed in the normal kidney and it is not found in renal tumors of BHDS patients [14, 34, 36, 47-50]. The germline *FLCN* gene mutation detection rate in BHDS patients is estimated to reach 84 to 88% of patients [21, 51]. The *FLCN* gene consists of 14 exons and most of the mutations have been reported in exon 4-14 [21, 51, 52] (Fig. 2). The hotspot of *FLCN* gene mutation is considered to be located in exon 11 [21, 51]. The mutation patterns of the *FLCN* gene consist of a splice site in introns, deletions, insertions, nonsense, deletion/insertion and missense [21, 51]. Insertions or deletions in this region were found in more than 40% of BHDS families [27, 48]. Intragenic deletions and duplication in the *FLCN* gene have also been identified in BHDS lacking the *FLCN* gene mutation [53]. Two hits represented by germline mutation in one allele and followed by somatic mutation (53%) in the other allele or loss of heterozygosity (17%) at the *FLCN* gene locus in the other allele cause BHDS-related renal tumors [34]. BHDS-related renal tumors are genetically distinct from other renal tumors including chromophobe RCC and oncocytoma. Additionally, increased expression of mitochondria- and oxidative phosphorylation-associated genes has been described in BHDS-derived renal tumors [54]. The mechanism leading to damage of the *FLCN* gene that leads to renal tumors remains unknown [55]. The wide spec-

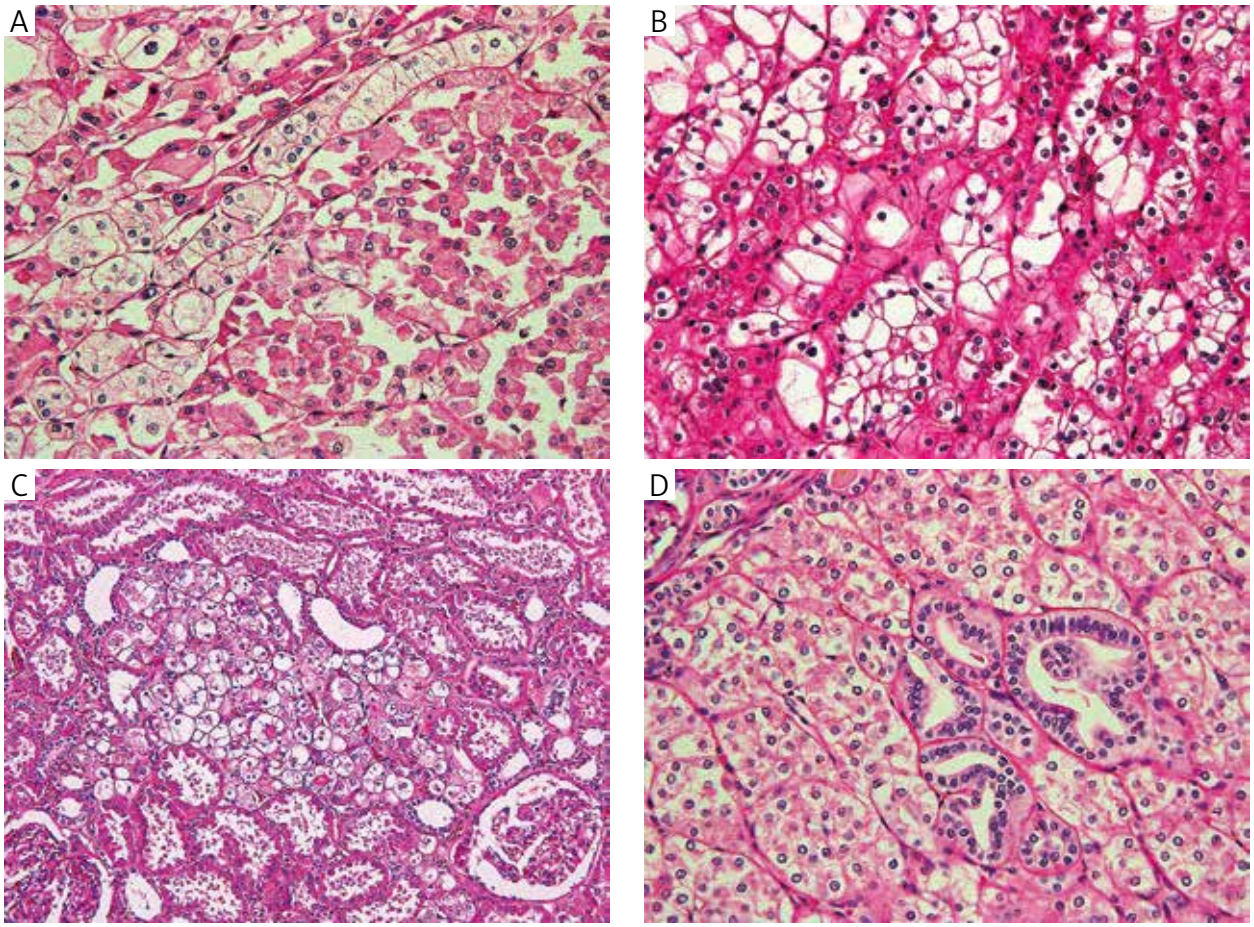

Fig. 1. Microscopic findings of BHDS-associated renal tumor. **A)** Hybrid oncocytic tumor has discrete areas of chromophobe RCC (left) and oncocytoma (right). **B)** In hybrid oncocytic tumor, clear cell change of neoplastic cells is noted. **C)** Renal oncocytic change with focal clear cell change is seen in the grossly normal-looking renal parenchyma. **D)** Small papillary tufts are often observed in the peripheral area of the tumor

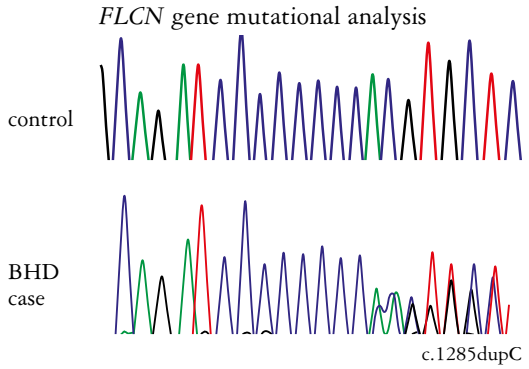

Fig. 2. Direct sequencing mutational analysis of *FLCN* gene in peripheral blood leucocytes of a BHDS patient. The *FLCN* gene mutation (cytosine duplication) is observed in exon 11

trum of renal histological types suggests that the *FLCN* gene may play a vital role in the differentiation process of renal tubular cells [20]. Namely, *FLCN* gene mutation affects the progenitor cells of proximal and distal tubules and collecting ducts, and gene mutation alters the composition of the extracellular matrix, producing structural or microenvironmental abnormalities that affect these tubular cells, and lead to uncontrolled cellular proliferation [48]. The *FLCN* gene is thought to be involved in energy and/or nutrient sensing through AMPK and mammalian target of rapamycin (mTOR) signaling [56].

Phenotype-genotype correlation

So far, no apparent genotype-phenotype correlations have been recognized [21, 31]. However, Schmidt *et al*. suggest that germline deletion of cytosine at exon 11 in the *FLCN* gene may be related to the occurrence of fewer renal tumors in BHDS patients than those associated with insertion of cytosine at the same hotspot mutation [51].

FLCN gene abnormalities leading to syndromes other than BHDS

The germline *FLCN* gene mutation was detected in 4.3% of patients with apparent nonsyndromic clear cell RCC susceptibility [57]. Somatic *FLCN* gene inactivation may occur in a subset of clear cell RCCs and colorectal cancer [58]. Loss of heterozygosity at the *FLCN* gene locus and promoter methylation of the *FLCN* gene were identified in 36% and 28% of various subtypes of sporadic renal tumors, respectively. These results suggest that the *FLCN* gene may play a major role in renal cancer tumorigenesis [59]. However, it should be noted that *FLCN* gene mutations are only rarely found in sporadic chromophobe RCC or renal oncocytoma [60].

Differential diagnosis

Renal oncocytosis associated with renal failure/hemodialysis or renal sporadic oncocytosis should be strictly distinguished from BHDS by checking the detailed clinical information including family history and associated disease [61]. In renal oncocytosis of sporadic type, no mutation of the *FLCN* gene has been identified so far [62]. When the renal tumor is solitary, and family history or associated diseases are absent, sporadic hybrid oncocytic/chromophobe tumor should be listed in the differential diagnosis [32, 63]. A number of previously described occurrences of familial oncocytoma have been found to have BHDS [41].

Clinical management and therapy

The clinical surveillance of BHDS patients should be initiated at the age of 20 years with focus on renal tumor occurrence [12]. CT scan is more sensitive than ultrasound sonography, but repeated CT scanning would cause an unacceptably high cumulative radiation dose [12]. Accordingly, annual renal MRI is recommended as the acceptable surveillance modality [12]. The same as renal tumors of other familial syndrome are managed [14], mere close observation should be undertaken until the largest tumor size reaches 3 cm. When the largest tumor exceeds 3 to 4 cm in the largest diameter, nephron-sparing surgery should be considered [12, 14, 25, 64-66]. If partial nephrectomy is not technically suitable, one-time radical nephrectomy should be performed. For lesions smaller than 3 cm, cryoablation or radiofrequency ablation might be preferred [12]. Ablative therapies including cryoablation or radiofrequency ablation may be suitable for patients with multiple small renal tumors such as familial syndrome [67]. As the *FLCN* gene is thought to be involved in energy sensing through the AMPK and mTOR pathways, mTOR inhibitors might be effective in patients with local recurrence or distant metastases [12, 42, 43, 56, 65, 68]. Patients with BHDS-associated renal tumors should be more aggressively managed than those with non-BHDS-associated renal tumors because of their histological discordance [69]. Early molecular diagnosis in families of BHDS facilitates the management and prevention of RCC [42].

Prognosis

Renal tumors associated with BHDS usually pursue a favorable clinical course, probably because the clinical behavior of hybrid oncocytic tumor, chromophobe RCC, and oncocytoma is usually not aggressive. Tumors are also mostly disclosed at a low clinical stage [5, 18, 40]. The clinical behavior of hybrid oncocytic tumor is still entirely uncertain and should

be proved by studies with available long follow-up. It may be reasonable to assume that renal oncocytic tumors exhibit biological behavior between oncocytoma and low-grade chromophobe RCC [8]. However, some cases have had metastases or a dismal outcome. The presence of clear cell components in renal tumors may reflect the worse prognosis [5, 15, 25, 70].

Future perspectives

We recently reported a case of multiple chromophobe RCCs with renal angiomyolipoma. However, we could not identify the *FLCN* gene mutation in this case [71]. On the one hand, a close relationship between BHDS and tuberous sclerosis complex in the common pathway through mTOR and clinical overlapping has been reported [38, 39, 72]. On the other hand, multiple chromophobe RCCs have been described in germline PTEN mutation Cowden syndrome [73]. In order to elucidate the relationship among BHDS, tuberous sclerosis complex and Cowden syndrome, a further examination in a large cohort study will be required.

Folliculin negatively regulates the AMPK/mTOR pathway, via complex formation with folliculin interacting proteins 1 and 2 (FNIP1 and FNIP2) to bind the g-subunits of AMPK [56, 74, 76-78]. Thus, enhancement of mTORC1 and mTORC2 functions may provide a novel therapeutic strategy for patients with BHDS. Additionally, mTOR inhibitors including rapamycin will also be potential therapeutic agents in the near future [76, 79].

The authors declare no conflict of interest.

This study was in part supported by a Grant-in-Aid from the Japanese Ministry of Welfare and Labor (to M. Furuya and Y. Nakatani).

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