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Review

Renal hybrid oncocytic/chromophobe tumors - A review

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Summary. Hybrid oncocytic/chromophobe tumors (HOCT) occur in three clinico-pathologic situations; (1) sporadically, (2) in association with renal oncocytomatosis and (3) in patients with Birt-Hogg-Dubé syndrome (BHD). There are no specific clinical symptoms in patients with sporadic or HOCT associated with oncocytosis/oncocytomatosis. HOCT in patients with BHD are usually encountered on characteristic BHD clinicopathologic background. Sporadic HOCT are composed of neoplastic cells with eosinophilic oncocytic cytoplasm. Tumors are usually arranged in a solid-alveolar pattern. Some neoplastic cells may have a perinuclear halo, with no raisinoid nuclei present. HOCT occurring in patients with oncocytomatosis are morphologically identical to sporadic HOCT. HOCT in BHD frequently display 3 morphologic patterns, either in isolation or in combination; (1) An admixture of areas typical of RO and CHRCC, respectively, (2) Scattered chromophobe cells in the background of a typical RO, (3) Large eosinophilic cells with intracytoplasmic vacuoles. The immunohistochemical profiles of HOCT in all clinicopathologic and morphologic groups differ slightly. The majority of tumors express parvalbumin, antimitochondrial antigen and CK 7. CD117 is invariably positive. HOCT show significant molecular genetic heterogeneity. The highest degree of variability in numerical chromosomal changes is present in sporadic HOCT. HOCT in the setting of oncocyto-matosis have revealed a lesser degree of variability in the chromosomal numerical aberrations. HOCT in patients with BHD display *FLCN* gene mutations, which are absent in the other groups. HOCT (all three clinicopathologic groups) seem to behave indolently, as no evidence of aggressive behavior has been documented. However, no report with follow up longer than 10 years has been published.

Key words: Kidney, Oncocytosis, Sporadic hybrid tumor, Chromophobe renal cell carcinoma, Oncocytoma, Birt-Hogg-Dubé syndrome

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Introduction

Classification of renal tumors with eosinophilic granulated oncocytoid cytoplasm is commonly a challenging task and gives rise to complex differential diagnostic considerations. Entities that need to be considered are chromophobe renal cell carcinoma (CHRCC), renal oncocytoma (RO), the oncocytic variant of papillary renal cell carcinoma (OPRCC) and the eosinophilic/granular variant of clear cell (conventional) renal cell carcinoma (CRCC). In addition, there exists a subset of oncocytic renal neoplasms which do not fit into any of the above diagnostic categories (oncocytic RCC, unclassifiable). Another group of renal tumours with oncocytic/oncocytoid features is composed of neoplasms which show histomorphological characteristics of both CHRCC and RO - hybrid oncocytic/chromophobe renal tumors (HOCT).

Apart from evoking practical issues of sampling, fixation etc, the designation hybrid tumor in principle, give rise to two problems; 1) wherther these tumors should display features in between RO and CHRCC or 2) wherther the ratiolale for this designation (hybrid) should be attributed to neoplasms which show a collision-pattern, i.e. that the tumor is composed of

different areas that show features of both RO and CHRCC. Notwithstanding this nosological discussion, there are several published studies on this group of renal parenchymal neoplasms. Interesting (and relevant for this topic) is the fact that renal carcinomas composed of areas with histomorphological features of both CRCC and PRCC have been documented (Mai et al., 2006; Haudebourg et al., 2010). The authors also substantiated this with molecular genetic data. A similar classification dilemma was recently highlighted by a case presented by Caamano et al. Their case was a tumor composed of an obvious CHRCC harboring a well-recognizable PRCC (Caamano et al., 2012)

There are few studies on HOCT. In essence, HOCTs occur in three clinico-pathologic scenarios; (1) sporadically, (2) in association with renal oncocytosis/ oncocytomatosis and (3) in patients with Birt-Hogg-Dubé syndrome (BHD). From the data published so far, it seems that tumors from all three groups share similar morphologic (solid-alveolar architecture, large eosinophilic cells with occasional perinuclear clearing - but no raisinoid nuclei, presence of cells with abundant pale cytoplasm) and immunohistochemical features. However, it appears that the spectrum of genetic aberrations displayed by HOCTs is wide and variable (Warfel and Eble, 1982; Tickoo et al., 1999; Pavlovich et al., 2002; Adley et al., 2006; Mai et al., 2005; Delongchamps, et al., 2009; Gobbo et al., 2010; Petersson et al., 2010).

Clinical presentation

HOCT occurring sporadically and in the setting of BHD occur in adults with no sex predilection (Pavlovich et al., 2002; Adley et al., 2006; Mai et al., 2005; Petersson et al., 2010; Waldert et al., 2010). This is also true for HOCTs associated with oncocytosis/ oncocytomatosis (Warfel and Eble, 1982; Tickoo et al., 1999; Al-Saleem et al., 2004; Cossu-Rocca et al., 2008; Gobbo et al., 2010).

There are no specific clinical signs and/or symptoms in patients with sporadic or HOCT associated with oncocytosis/oncocytomatosis. In contrast, HOCT in patients with BHD may present with a spontaneous pneumothorax associated with pulmonary cysts and patients most often have multiple facial fibrofolliculomas or trichodiscoma (Adley et al., 2003).

Pathological findings

Macroscopy

Sporadic HOCTs are unilateral, solitary tumors whereas HOCTs occurring within the setting of BHD or oncocytosis/oncocytomatosis frequently present as bilateral and/or multiple lesions. The tumors are usually well circumscribed, non-encapsulated with homogenous tan to brown cut surfaces. Necrosis is not frequently seen. Central fibrotic scar/fibrous strands may be present (Warfel et al., 1982; Tickoo et al., 1999; Pavlovich et al., 2002; Adley et al., 2006; Mai et al., 2005; Delongchamps et al., 2009; Gobbo et al., 2010; Petersson et al., 2010). The majority of HOCTs in all settings are stage pT1 or pT2 (TNM classification, UICC 2009).

Histopathology

Sporadic HOCTs are composed of neoplastic cells with mildly pleomorphic nuclei and abundant granular eosinophilic "oncocytoid" cytoplasm. Tumors are usually arranged in a solid-alveolar pattern. Some neoplastic cells may have a perinuclear halo with the presence of occasionally binucleated cells. These nuclear changes should however only be found focally and no raisinoid nuclei (as seen in classic CHRCC) should be present. Mitoses are exceedingly rare and atypical mitoses are absent. In most cases a significant component of the tumor cells resemble cells of renal oncocytoma, i.e. with perinuclear cytoplasmic clearing and round nuclei with sharply demarcated nuclear membranes. Occasional small tubules may be present, but prominent/widespread tubule formation is not a characteristic feature of HOCT.

From a morphologic point of view it seems that HOCTs occurring in patients with oncocytosis/ oncocytomatosis are identical to sporadic HOCT. HOCTs in oncocytosis more likely do not represent a stage of progression between RO and CHRCC.

HOCTs in BHD frequently display 3 morphologic patterns, either in isolation or in combination:

1: An admixture of areas typical of RO and CHRCC

2: Scattered chromophobe cells in the background of a typical RO

3: Large eosinophilic cells with intracytoplasmic vacuoles.

The neoplastic nuclei are frequently pleomorphic and may occasionally acquire a "raisinoid" shape (Pavlovich et al., 2002; Mai et al., 2005; Murakami et al., 2007; Delongchamps et al., 2009; Gobbo et al., 2010; Petersson et al., 2010).

Immunoprofile

The immunohistochemical profiles of HOCTs in the three different groups differ slightly. However, the majority of tumour cells in most HOCTs express parvalbumin, antimitochondrial antigen (AMA) and cytokeratin (CK)7. CD117 is invariably positive in all three groups.

Sporadic HOCTs are positive for cytokeratins (CK); AE1-AE3, epithelial membrane antigen (EMA), AMA with diffuse positivity and with perinuclear clearing. Tumors are frequently focally positive for vimentin (single cells). Mostly, tumors are positive for CK 7, E-Cadherin, CD117, and parvalbumin. AMA is diffusely positive with focal perinuclear halos. There is usually a lack of reactivity for racemase, CK 20, CD10 and

carbonic anhydrase IX (Mai et al., 2005; Petersson et al., 2010).

HOCTs associated with oncocytosis/oncocytomatosis are positive for parvalbumin and AMA, with variable positivity for CK 7 and S100A1. (Tickoo et al., 1999; Gobbo et al., 2010; Kuroda et al., 2012). CD117 is invariably positive (membranous positivity) in HOCTs from this group. The intensity of staining is not constant and negative areas are frequently seen (personal unpublished observation).

HOCTs in BHD are positive for AMA, variably positive for CK 7, parvalbumin, and cytokeratins (AE1-AE3). Single cells are usually positive for vimentin.

From the above mentioned immunohistochemical findings it is obvious that there is not specific immunohistochemical staining pattern that can reliably distinguish HOCTs from RO or CHRCC.

Ultrastructure

Neoplastic cells of sporadic HOCTs contain numerous mitochondria of varying size and shape (mostly with lamellar cristae). Sparse microvesicles with amorphous lamellar content may be present, but there is no abundance of microvesicles in the cytoplasm (Petersson et al., 2010). Ultrastructural features of sporadic HOCTs have also been described by Barcena et al., (2010). The authors described so-called "oncocytomas" with mitochondria containing "tubulovesicular cristae". According to Barcena, these mitochondria are a highly characteristic feature of CHRCC. In contrast, mitochondria in RO are characterized by the presence of pilled lamellar cristae.

Chen et al, have characterized HOCTs in patients with oncocytosis/oncocytomatosis. The authors describe that the cytoplasm of the tumor cells in the RO-like areas contained abundant mitochondria with lamellar cristae, whereas the cytoplasm in the chromophobe RCC-like area showed a significantly diminished number of mitochondria with lamellar cristae, increased amount of glycogen and no evident cytoplasmic microvesicles (Chen et al., 2003). Also, Nagashima performed an ultrastructural analysis of oncocytomas in oncocytosis/oncocytomatosis. In his report, neoplastic cells contained numerous small uniform mitochondria, but no microvesicles (Nagashima et al., 2005).

We are not aware of any study dealing with ultrastructure of HOCTs in BHD in the English literature.

Molecular-genetic features

Although HOCTs show significant molecular genetic heterogeneity both within and between the different groups, it appears that the highest degree of variability in numerical chromosomal changes is present in sporadic HOCTs. HOCTs in the setting of oncocytosis/oncocytomatosis have revealed a lesser degree of variability in the numerical aberrations of chromosomes and display a pattern more akin to that seen in RO.

A useful and important diagnostic molecular genetic feature of HOCTs in patients with BHD is the presence of *FLCN* gene mutations, which are absent in the other groups.

Sporadic HOCTs are characterized by multiple numerical aberrations (both mono- and polysomies), namely of chromosomes 1, 2, 6, 9, 10, 13, 17, 20, 21, 22. According to Petersson et al., monosomy of chromosome 20 is the most commonly encountered numerical aberration, followed by monosomy of chromosomes 6 and 9. Monosomy of chromosome 20 is

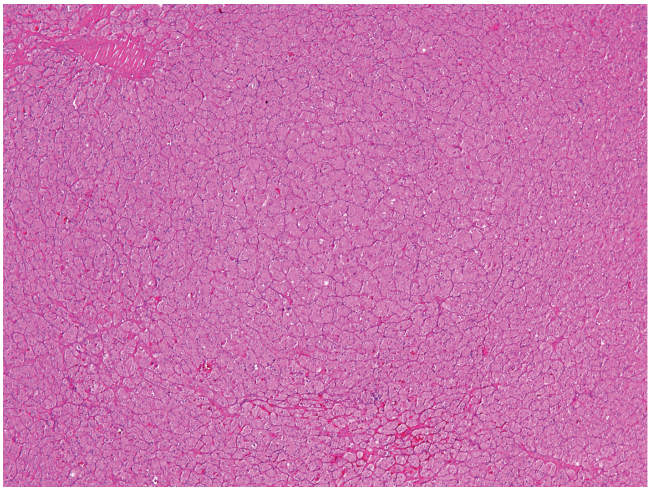

Fig. 1. Sporadic HOCT: Solid to solid/alveolar architecture. HE, x 40

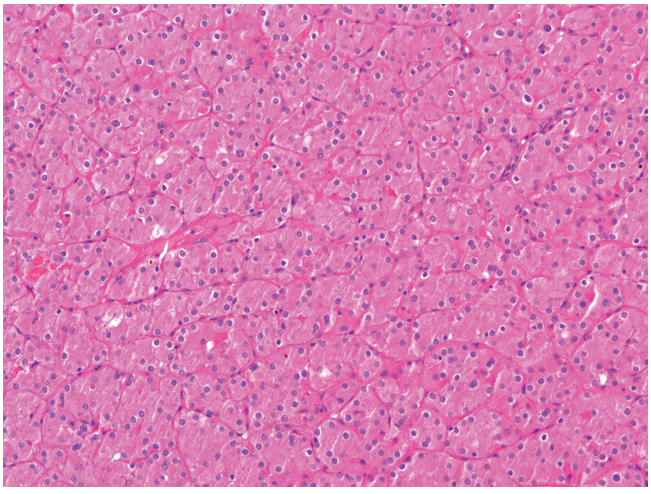

Fig. 2. Sporadic HOCT: No raisinoid nuclei typical for chromophobe RCC could be seen, however prominent perinuclear clearing is focally present. HE, x 100

a rather unusual feature for renal cell tumors and highly unusual both for both CHRCC and RO. No mutations in *VHL* gene, *c-kit, PDGFRA* and no loss of heterozygosity (LOH) for the small arm of chromosome 3 (3p) were detected (Petersson et al., 2010).

HOCTs associated with oncocytosis/oncocytomatosis are characterized by a variable chromosomal profile. Tumors usually show no chromosomal losses of chromosomes 1, 2, 6, 10, 17. However, losses of chromosomes 1, 14, 21 and Y have been documented (Al-Saleem et al., 2004; Cossu-Rocca et al., 2008; Gobbo et al., 2010).

HOCTs in BHD also display a variable chromosomal profile. Multiple abnormalities have been reported affecting chromosomes 2, 3, 4, 5, 6, 13 and 18. No HOCT in the setting of BHD has been shown to harbor loss of chromosome 1 or translocation of 11q13. The most prominent molecular-genetic feature of HOCT associated with BHD setting is high expression of genes associated with mitochondria and oxidative phosphorylation (*OXPHOS*) and germline mutations in the *FLCN* gene. LOH 3p has been rarely reported (Pavlovich et al., 2002; Adley et al., 2006; Klomp et al., 2010).

Prognosis

HOCTs (all three groups) seem to behave indolently, as no evidence of aggressive behavior has been documented. However, it is not possible to find any report with long-term follow up (10 or more years) in the literature (Tickoo et al., 1999; Pavlovich et al., 2002; Mai et al., 2005; Adley et al., 2006; Kesik et al., 2010; Petersson et al., 2010; Abbosh et al., 2011; Nagashima et al., 2012).

Aggressive, metastatic renal tumors have been referred to in BHD. However, these tumors were not HOCTs but clear cell RCC or clear cell RCC with chromophobic, tubular and papillary areas (Pavlovich et al., 2005). Another type of renal tumor with metastatic activity within BHD was referred to by Houweling et al., In their series, 3 cases of metastasizing renal tumor composed of cells with eosinophilic cytoplasm and morphologic characteristics of both CRCC and CHRCC (one of them with sarcomatoid transformation) were reported (Houweling et al., 2011).

Pathogenesis

The etiopathogenesis of sporadic HOCTs remains unknown. It seems that these tumors are not associated with any particular pathologic condition, like end-stage kidney disease/long term dialysis, hereditary syndromes (*VHL* gene mutations, *C-MET* mutations, tuberous sclerosis complex) etc.

Birt-Hogg-Dubé syndrome (BHD) is an autosomal dominant genodermatosis characterized by multiple fibrofolliculomas/trichodiscomas in the head and neck region and upper trunk area, associated with an increased risk of developing renal neoplasia, pulmonary cyst and spontaneous pneumothorax (Pavlovich et al., 2002; Furuya et al., 2012). BHD is associated with mutations in the folliculin (*FLCN*) gene mapped to chromosome 17p12q11 (Adley et al., 2006; Imada et al., 2009). In the renal cortex of patients with BHD there are frequently multiple microscopic foci of aggregated oncocytic cells. The most common renal neoplasm associated with BHD is the hybrid oncocytic/chromophobe tumors. However, conventional (and pure) clear cell carcinomas, oncocytomas, chromophobe renal

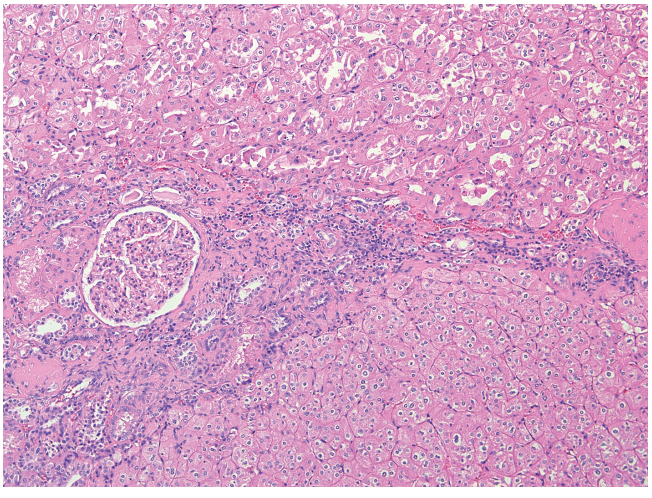

Fig. 3. HOCT in association with oncocytosis/oncocytomatosis. Upper tumor is HOCT, lower tumor display features typical for chromophobe RCC. HE, x 100

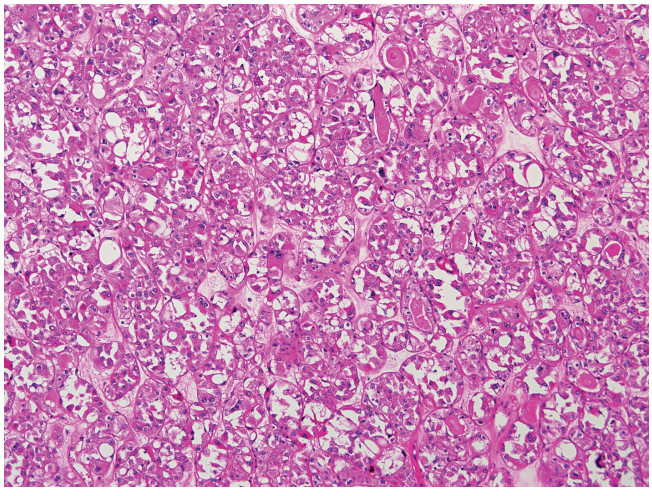

Fig. 4. Solid alveolar pattern typical for HOCT in BHD patient. Architecture resembles RO, but cells have prominent intracytoplasmic vacuoles and organelles pushed to the periphery. HE, x 100

cell carcinomas, "tubopapillary clear to eosinophilic cell RCC" and papillary renal cell carcinomas have also been reported in the setting of BHD (Pavlovich et al., 2002, 2005; Murakami et al., 2007; Gatalica et al., 2009; Kluijt et al., 2009).

The term "renal oncocytomatosis" was used by Warfel in 1982 for a case with multiple ROs and oncocytic changes in renal tubules (Warfel and Eble, 1982). In 1999, Tickoo used the term oncocytosis to describe an almost identical lesion. This term has been widely accepted (Tickoo et al., 1999) and both terms are currently used in the literature (Sydor et al., 2009). Renal oncocytosis is defined as a diffuse replacement of the renal parenchyma by numerous oncocytic tumors including HOCTSs, chromophobe renal cell carcinomas and ROs and oncocytic change in non-neoplastic renal parenchyma (Tickoo et al., 1999). According to a large, recently published study, HOCT is the most common renal tumor type associated with oncocytosis/oncocytomatosis (Adamy et al., 2011). Renal oncocytosis/oncocytomatosis may arise in a sporadic setting, in patients with chronic renal failure and long-term hemodialysis or in association with Birt-Hogg-Dubé (BHD) syndrome (Leroy et al., 2001; Shiga et al., 2002; Kuroda 2003; Nagashima et al., 2005; Mazzucchelli et al., 2008; Tickoo et al., 2009).

Differential diagnosis

The solid or solid-alveolar architecture of HOCTs resembles renal oncocytoma. Renal oncocytomas may show a wide range of morphological appearances, including variants composed of voluminous cells, smaller cells arranged in variable patterns. ROs may be solid, tubular and stroma-rich. The presence of perinuclear haloes in HOCT cases is typically not seen in oncocytomas. The so-called small-cell variant of RO differs from HOCT by being composed of a predominant population of small cells, mostly arranged in solid alveolar pattern. The formation of pseudorosettes may be seen in these tumors (Hes et al., 2001; Petersson et al., 2011). In HOCTs composed of both oncocytic and chromophobe areas, the dual morphologic character is obvious on routine histologic examination. Adequate sampling of these tumors is of paramount importance. The molecular-genetic features of HOCT differ from that of RO. Some oncocytomas are composed of a mixed population of cells with normal as well as abnormal karyotypes (Kovacs et al., 1987, 1989). No numerical chromosomal changes were detected using comparative genomic hybridization in RO with renal vein extension (Hes et al., 2008). However, loss of chromosomes 1 and 14 have been reported in RO (Presti et al., 1996; Herbers et al., 1998). According to recently published studies, 50-60% of RO show a normal chromosomal karyotype . Approximately 40% of ROs show complete or partial loss of chromosome 1, followed by loss of chromosome Y (15% of ROs) and monosomy of chromosome 14 (15%). Also, trisomy of chromosome 7 and structural rearrangements of 11q12-q13 have been reported (Hagenkord et al., 2011). However, even though ROs display variable genetic changes, they lack the numerical chromosomal aberrations characteristically seen in sporadic HOCTs. Moreover, ROs lack mutations in the *FLCN* gene (Picken, 2010; Yusenko, 2010). A diagnostically difficult situation may be encountered in the setting of oncocytomatosis, where numerous RO are present.

The most difficult differential diagnostic consideration of a HOCT is CHRCC. The neoplastic cells in CHRCC may be arranged in variable patterns, ranging from solid-alveolar to adenomatoid/microcystic. The morphological features of neoplastic cells are characteristic. Although perinuclear halos and occasional binucleated neoplastic cells are common in HOCT, no raisinoid nuclei typically present in CHRCC are present in any of the morphologic variants (Brunelli et al., 2005; Hes et al., 2005; Amin et al., 2008). Recognition of such nuclei is crucial for establishing a diagnosis of CHRCC (Tickoo and Amin, 1998). Although immunohistochemistry could serve as a valuable differential diagnostic tool, in some cases it does not work. For example, antibodies like CD117, CK 7, Claudin-7, Claudin-8, CD82 (KAI1), epithelial-related antigen (ERA), epithelial-specific antigen (ESA) and S1001A have been put forward as being useful for the differential diagnostic work-up (Osunkoya et al., 2009; Yusenko and Kovacs 2009; Ohe at al., 2012). However, in cases with overlapping morphology, as is the case with HOCT, the interpretation of the immunohistochemical examinations may be complicated.

Another such difficult instance is the diagnosis of the so-called "oncocytic variant" of CHRCC which has been recently published (Yamaguchi et al., 2010). This

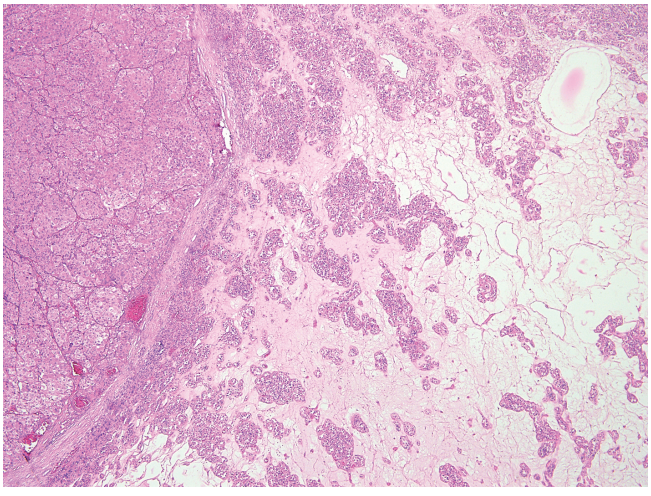

Fig. 5. Tumor in BHD patient composed of CHRCC area, which is surrounded by structures compatible with renal oncocytoma. Sharp border between both neoplastic components is clearly visible. HE, x 40

tumor was composed of oncocytic cells with abundant mitochondria and round nuclei. This tumor exhibited a dominant tubular pattern and lacked perinuclear haloes. FISH analysis of the tumor revealed monosomies of chromosomes 7, 10, 13 and 17. Another study has shown that some CHRCCs may contain oncocytoma-like areas (Amin et al., 2008). Already in 1997 Erlandson et al suggested the existence of possible oncocytic variant of CHRCC (Erlandsson et al., 1997). However this variant has not been widely accepted since many investigators have considered that tumors featuring this morphology should be categorized as eosinophilic variant of CHRCC.

Another renal cell carcinoma that should be taken into consideration is the oncocytic variant of papillary RCC. Oncocytic papillary RCC shows at least focal definitive fibrovascular cores and displays strong immunohistochemical positivity for racemase. However, up to 80% of the tumor volume may display a solid architecture and in such cases, well-performed sampling is critical (Hes et al., 2006). Usually it is possible to detect smaller or larger areas composed of foam cells. No perinuclear halos or raisinoid nuclei are present. Moreover, nearly all papillary RCCs, including the oncocytic variant, display trisomy for chromosomes 7 and 17 (Lefevre et al., 2005; Hes et al., 2006). Polysomy of chromosome 7 or 17 (not in combination) was occasionally shown in HOCTs, but also in combination with other numerical changes not characteristically seen in PRCC (Petersson et al., 2010). The same is true for those ROs, which display trisomy of chromosome 7 (Hagenkord et al., 2011).

The eosinophilic granular variant of clear cell RCC is composed of large eosinophilic granular cells. The granular variant of clear cell RCC is easily discriminated based on the presence of diffuse strong vimentin and at least focally strong CD10 positivity within tumorous cells. Also absence of LOH for 3p and no mutations in the *VHL* gene can help in the differential diagnosis between HOCT and granular variant of clear cell RCC.

The diagnosis of HOCT on a core biopsy poses significant difficulties and is frequently impossible. Sporadic HOCT are extremely rare tumors. It is possible that sporadic HOCT could be erroneously diagnosed as RO (from core biopsy). However, from statistical point of view such possibility is unlikely and do not justify a surgical intervention for all RO diagnosed on core biopsy (Lhermitte and de Leval 2012).

From a practical point of view, we would recommend following algorithm for examination of cases suspected of being HOCT:

It is necessary to consider 3 possibilities in the differential diagnosis of HOCTs:

1. Rule out BHD (anamnesis, radiographic examinations, *FLCN* gene examination).

2. Rule out a history of hemodialysis or chronic renal failure causing oncocytosis/oncocytomatosis.

3. Rule out oncocytosis/oncocytomatosis by examination of gross specimen and/or radiographic documentation (importantly, even cases associated with oncocytosis/oncocytomatosis could be part of BHD).

4. After resolving the 3 above listed points it is possible to make diagnosis of sporadic HOCT.

Conclusion

From a morphological point of view, there are similarities between HOCT on the one hand and RO and CHRCC on the other hand. However, all 3 clinicopathological subtypes of HOCT have significantly different molecular-genetic profiles from both RO and CHRCC. Sporadic HOCTs frequently show monosomy of chromosome 20 (among multiple chromosomal numerical aberrations), which is highly unusual for any known renal cell tumor including CHRCC and RO. Also, HOCT in oncocytosis/oncocytomatosis and HOCT in patients with BHD differ from CHRCC and RO on a molecular-genetic level (usually no losses on chromosomes 1, 2, 6, 10, 17, *FLCN* gene mutation). To date, no single case report describing aggressive or metastatic HOCT has been published.

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