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The impact of germline BHD mutation on histologic concordance and clinical management of patients with bilateral renal masses and known unilateral oncocytoma

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Abstract

Introduction and Objective—Managing patients presenting with oncocytoma in the setting of bilateral renal masses is a challenging scenario. Nevertheless, pathologic concordance of oncocytic neoplasm in one kidney with tumors in the contralateral kidney is not known. We aim to evaluate the influence of germline Birt-Hogg-Dubé (BHD) mutation on concordance rates to assist in management of these patients.

Methods—We reviewed records of the NIH patients between 1983 and 2009 having bilateral renal masses, known pathology bilaterally, and presence of oncocytoma or oncocytic neoplasm in at least one kidney. The presence of oncocytoma or oncocytic neoplasm in two renal units was considered concordant. Demographic, pathological and clinical data were collected.

Results—The patient population consisted of 40 patients: 23 with BHD and 17 patients without diagnosis of BHD. Patients with BHD were younger ($p < 0.01$) but there were no other differences between two groups. However, patients with BHD had a statistically lower histologic concordance between bilateral masses when compared to patients without the diagnosis of BHD (Fisher's exact test, $p < 0.01$). Additionally, the subgroup of patients ($n = 8$) without BHD who had multifocal renal masses demonstrated 100% oncocytoma concordance between renal units.

Conclusions—In patients with bilateral renal masses BHD patients have significantly lower histologic concordance rates compared to patients without BHD. Patients with BHD should be monitored and managed differently than patients without detected genetic mutations, especially those with multifocal oncocytomas. Genetic testing for BHD should be considered in the algorithm for management of patients with bilateral renal masses and known oncocytoma.

Keywords

oncocytoma; oncocytic tumor; Birt-Hogg-Dubé; concordance; bilateral renal tumors

Bilateral renal carcinoma has been reported to be present in 0.8 to 11% of renal cancer patients.^{1–3} Identifying specific genetic alterations in patients with bilateral renal involvement may direct clinical decisions regarding surveillance and timing for surgical intervention. Although the genetic basis for patients with bilateral, multifocal renal masses is not always identified, a number of hereditary renal cancers syndromes and their phenotypic characteristics have been described.^{4–5} While the majority of these hereditary kidney cancer syndromes are characterized by a single renal tumor histologic type, BHD is unique in its spectrum of tumors including hybrid oncocytic, chromophobe, clear cell, and oncocytoma.⁶

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Oncocytomas account for 3–7% of all renal neoplasm and are typically solitary and sporadic.⁷ Alternatively, oncocytomas have been reported to be bilateral, multifocal, and familial although specific genetic alternations have not yet been identified.⁸ The management of the contralateral kidney in patients with bilateral renal tumors when oncocytoma or oncocytic neoplasm is pathologically confirmed in one kidney is not well established. Current options include observation, biopsy, ablation or surgical extirpation. The goal of this study is to evaluate the concordance of renal pathology in patients with bilateral renal masses presenting with at least one oncocytoma or oncocytic neoplasm. We also establish the algorithm for evaluation and management of these patients.

Materials and Methods

The database of patients evaluated at the Urologic Oncology Branch of the National Cancer Institute (NCI) between 1983 and 2009 was queried to identify a cohort of patients with the following inclusion criteria: 1) the presence of bilateral renal masses; 2) a pathology report reviewed at the NCI available from each renal unit; and 3) the diagnosis of oncocytoma or oncocytic neoplasm in either kidney. The diagnosis of oncocytic neoplasm was given to homogeneous oncocytoma-resembling tumor with eosinophilic cells and occasionally some nuclear irregularity that was not felt to be classic oncocytoma, but was likely a benign neoplasm.

Demographic, pathologic, and clinical data were collected through chart and operative report review. Germline testing for BHD mutation has been described previously.⁹ Briefly, after DNA was isolated, intronic primers were designed for to amplify coding sequences and splice junctions of probands with subsequent sequence analysis of the 14 coding exons. BHD germ line mutation testing identifies mutations in over 90% of affected patients.^{10–11} Patients with presumed Familial Renal Oncocytoma (FRO) or those with histologically-confirmed family history of renal oncocytoma were eliminated from final analysis because of their previously described high tumor concordance rates.¹²

The term “concordance” was used if the pathological diagnosis between bilateral renal tumors were identical, i.e. only the oncocytoma or oncocytic neoplasm was present in each kidney. These tumors are histologically distinct from the hybrid oncocytic tumor, consisting of both oncocytoma and chromophobe renal cell carcinoma that has metastatic potential.¹³ Patients with any histologic diagnosis other than oncocytoma or oncocytic neoplasm in any of their renal masses were considered “discordant”. Tumors with mixed histology (presence of any other histology other than oncocytoma or oncocytic neoplasm) were also considered discordant.

The CCI was calculated and compared between patients with and without BHD. The index contains 19 categories of comorbidity, which are primarily defined using ICD-9 diagnosis codes using the original Charlson paper.¹⁴ The score reflects the cumulative increased likelihood of one-year mortality. Statistical analysis was performed using student t-test and Fisher's exact test. All tests were 2-sided and $p < 0.05$ was considered statistically significant.

Results

A total of 46 patients were identified that initially met the inclusion criteria. Twenty-three of the patients were found to **be affected by BHD**. Six patients with histologic-proven family history of oncocytoma were eliminated due to know high concordance rates leaving 17 patients in the “non-BHD” group. A total of 40 patients were included in the final analysis.

Patient demographics and tumor information listed in table 1. The only significant differences between patients with and without diagnosis of BHD were age ($p < 0.01$, Student

T-test) and the histologic concordance ($p < 0.01$, Fisher's exact test). The average size of the largest tumor was 4.9cm (range 2.6–8.5) in the BHD group and 5.3cm (range 1.6–8.5) in the non-BHD group. Correlation between contralateral pathology and tumor size was not observed. Percent Caucasian, percent male, total number of procedures, and tumor number were similar in both groups. Follow up data was available on 36 of 40 patients (90%). Mean overall follow up of patients with at least one follow up visit to NIH was 85.6 months (range 10–301). Three patients in each group developed de novo renal insufficiency (eGFR < 60) during follow-up. There were no patients who developed metastatic disease from their oncocytoma or oncocytic tumors. One patient in the BHD cohort (4%) developed metastatic RCC from a clear cell RCC and died of his disease.

There were a total of 100 procedures performed in these 40 patients including 55 procedures in the BHD group and 45 in the non-BHD group. The majority of the histologic diagnoses (73 of 80 units or 91%) were established from extirpative procedures (partial or total nephrectomy), while diagnosis in the remaining 7 renal units (9%) was established via core biopsy. Eight additional biopsies in the cohort were performed prior to ipsilateral partial nephrectomy, and the pathologic concordance between biopsy and final pathology in those eight kidneys was 100% (8/8).

Patients with BHD were statistically more likely to have discordant histologic disease when compared with patients without BHD, $p < 0.01$ (Fisher's Exact test). Nine of 23 patients (39%) in the BHD group had concordant oncocytoma or oncocytic tumors bilaterally as compared to 16 of 17 (94%) in the non-BHD group. In addition to oncocytoma and oncocytic neoplasm, additional tumor histology in the entire cohort included chromophobe renal cell carcinoma (RCC), clear cell RCC, papillary RCC, and hybrid oncocytic tumor. Within the BHD group, rates of fibrofolliculoma, pulmonary cysts, and renal tumor histology was similar to our prior reports.⁶ Other than the hybrid tumor unique to BHD, no oncocytoma or oncocytic tumor removed exhibited co-existing clear cell or papillary RCC.

Discordance in the BHD group consisted of a variety of tumors including clear cell, hybrid tumor, and chromophobe RCC. Discordance in the non-BHD group was found in only one patient: a clear cell RCC tumor in a patient with oncocytoma and presumed acquired renal cystic kidney disease found after nephrectomy. In patients without BHD and multifocal oncocytomas, there was 100% histologic concordance.

Discussion

Patients with bilateral renal masses and a known diagnosis of oncocytoma in one kidney present several management challenges in regards to treatment of the contralateral kidney. First, radiographic imaging modalities have not been consistently able to differentiate benign from malignant histology.¹⁵ Second, any procedure for tumor acquisition (biopsy or surgery) carries associated morbidity and cost. Third, performing extirpative renal surgery (open or laparoscopic, partial or total) on a patient with a high likelihood of benign histology is not rewarding for either the surgeon or the patient. Nevertheless, because of the lack of an ideal diagnostic modality, surgical intervention often remains the primary treatment for this patient population. Therefore, predicting the pathology of the contralateral renal tumor in patients with renal oncocytoma and bilateral renal masses may potentially impact treatment algorithms and steer urological surgeons towards a more aggressive or conservative management pathway.

Because of the unique referral patterns at the NIH, we typically see patients with bilateral and/or multifocal renal tumors. While renal oncocytoma is rarely reported to be bilateral and/or multifocal, its true incidence and prevalence has not been extensively evaluated in the

setting of bilateral renal masses. Over time we have evaluated a substantial number of this unique and challenging patient population allowing us to evaluate both the likelihood of histologic concordance as well as identify factors influencing these concordance patterns.

A search of specific genetic alteration in patients with bilateral multifocal renal masses has resulted in several well described renal cancer syndromes.^{5, 16} Unfortunately, specific genetic alterations responsible for familial renal oncocytoma associated with bilateral disease and a family history of oncocytoma have not yet been identified.¹² Chromosomal alterations such as a partial or complete loss of chromosomes 1 or Y have been suggested although it appears that these changes are more common in sporadic rather than familial renal oncocytomas. A molecular-genetic analysis from Junker et al suggested that 87% of familial oncocytoma were devoid of chromosomal instabilities.¹⁷

Inherited susceptibility to oncocytoma has been closely associated with Birt-Hogg-Dube syndrome. Originally described in 1977 and associated with familial renal tumors in 1999, BHD is known to be an autosomal dominant, inherited cancer syndrome in which affected individuals may have benign cutaneous fibrofolliculomas, pulmonary cysts and spontaneous pneumothorax, and renal neoplasms.¹⁸⁻¹⁹ BHD is associated with a variety of renal pathology including hybrid oncocytic tumor (tumor containing elements of oncocytoma and chromophobe RCC), chromophobe RCC, clear cell RCC, and pure oncocytoma.¹³ The *BHD* (*FLCN*) gene was mapped to chromosome 17p11.2 and further investigation led to the identification of the BHD gene encoding a protein named folliculin, important in regulation of the mTOR pathway.^{9, 20-21} Notably, 23 patients in our cohort tested positive for BHD during germline genetic screening.

There two major differences between patients testing positive or negative for BHD included patient age and the rates of histologic concordance between the two renal units. The significantly lower age of patients in the BHD group should be anticipated in patients with known germline alterations and a possible family history of renal disease.⁴ Nevertheless, when the Charlson comorbidity index and age adjusted CCI were calculated, no differences between the BHD and non-BHD group were found.

The significantly lower histologic concordance rates (39 vs. 94% $p<0.01$) when compared to the non-BHD group is certainly influenced by the spectrum of renal tumor histology found in patients with BHD.⁶ While the high positive BHD rate in our cohort is likely a reflection of our unique referral pattern, it may also be influenced by pathology-directed genetic screening, established in our department. In terms of its potential impact on management strategies the observation that patients without BHD had significantly higher pathologic concordance rates may be even more important. Among the non-BHD group, discordant histology was found in only one of seventeen patients (6%). In addition, in those in this group with bilateral multifocal renal masses, oncocytoma concordance rates were found in 100%. These findings suggest that a conservative, non-operative approach, in the non-BHD group may be warranted.

There are few reports that have addressed the histologic concordance rates in bilateral renal masses. Rothman et al. evaluated pathologic concordance of sporadic synchronous bilateral renal masses in the SEER database as well as in patients seen at Fox Chase Cancer Center, describing malignant concordance rates of 95% in both instances.²² Benign concordance rates were 67% but included only 6 patients. Patel et al reviewed their experience of 46 patients with bilateral sporadic renal tumors, describing an overall concordance rate of 76%.²³ In this series 3 of 5 patients (60%) with oncocytoma on one side had oncocytoma in the second tumor. The largest series describing the likelihood of benign bilateral histology was from Blute et al. who reported a 39% concordance rate in 23 patients.²⁴ Our overall

benign histology concordance rate (65%) is higher than the Blute et al. series but similar to the other published reports. Our cohort of 40 patients with oncocytoma and bilateral renal masses represents the largest reported series of bilateral benign tumors to date.

Based on the differences observed in histologic concordance we have suggested a management algorithm for patients who present with or develop bilateral renal masses with a known history of oncocytoma or oncocytic tumors. Figure 1 demonstrates our treatment approach. Initially, family history, dermatologic exam, and non-contrast chest CT should be obtained to evaluate for common manifestations of BHD. If any of these findings are positive, the patient is of a young age or has multifocal disease, they should be offered germline *BHD* mutation testing. Positive clinical suspicion or genetic testing for BHD should direct the management of the contralateral side. When the diagnosis of BHD is made, patients most often undergo active surveillance until the largest tumor reaches 3 cm, at which point the nephron sparing surgery is often recommended. To date, we have not observed a metastasis in a single patient with BHD managed with this approach. On the other hand, patients with bilateral, multifocal renal tumors with an oncocytoma who test negative for BHD and do not have phenotypic manifestations of BHD have high likelihood of having oncocytoma in the contralateral kidney and may be followed more conservatively. Patients with multifocal oncocytoma and bilateral disease are the most likely group to demonstrate oncocytic disease on the contralateral side. These patients would be best suited for active surveillance regardless of the tumor size. If the clinician or the patient is uncomfortable with either the size or the growth rate, renal biopsy rather than surgery first should be considered.

In cases of diagnostic uncertainty, one may consider a role of percutaneous renal biopsy. A report from Neuzillet et al in 2005 followed 15 patients with biopsy proven oncocytoma using radiographic surveillance.²⁵ Six patients ultimately required surgery because of initial tumor volume, growth rate (>5mm/year), or patient preference. One of the six (16%) had a co-existent chromophobe RCC within the oncocytoma, which was most likely a hybrid tumor associated with BHD (although formal testing was never done). No patients developed metastatic disease. This is consistent with recent reports demonstrating excellent survival of patients with chromophobe/oncocytoma lesions.²⁶ Neuzillet et al demonstrated annual growth rates of 0.7mm in the observed group and 2.4mm in the operated group suggesting that the natural evolution of oncocytoma is to increase in size and that growth rates may be useful criteria when considering surveillance vs. renal interventions such as renal biopsy or nephron sparing surgery.²⁵ In either event, patients negative for BHD have a higher likelihood of bilateral benign disease and should be considered for non-operative management whenever possible.

When using results of percutaneous core biopsies to develop treatment algorithms for patients with renal masses, the potential inaccuracy of this approach should be considered. Non diagnostic rates have been reported as high as 31% in some series.¹⁵ A recent review from Volpe and Jewett reported an accuracy of current renal tumor biopsy techniques in characterizing a lesion as over 90%.²⁷ In the present series we performed 15 renal biopsies, eight of which were eventually followed by a partial nephrectomy, with 100% concordance. In addition to the potential inaccuracy of renal biopsy, we should acknowledge additional limitations including the retrospective nature of the study and the relatively small sample size. Also, differences in pathologic tissue processing and tumor heterogeneity may have influenced our results. Finally, the reported mutation detection rate of 90% among known BHD families may potentially limit the accuracy of screening amongst patients.¹¹ However, to our knowledge this study represents the largest cohort evaluating this patient population with the longest follow up in the literature.

Conclusions

Patients with oncocytoma or oncocytic tumors and bilateral renal tumors may benefit from clinical and genetic testing for BHD. Patients without BHD tend to have excellent rates of pathologic concordance of the contralateral side and should be counseled towards a more conservative course of management. Conversely, BHD patients have significantly lower histologic concordance rates and should be managed more aggressively. Testing for BHD should be considered as a first step in the treatment algorithm of patients with bilateral renal masses and oncocytoma/oncocytic neoplasm on one side.

Acknowledgments

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Figure 1. Treatment management algorithm for patients with bilateral renal masses and oncocytoma/oncocytic tumor on one side.

Table 1

Patient characteristics and tumor information

	Patients with BHD	Patients without BHD	
N	23	17	P value
Age, yrs	52 (31–69)	64.5 (53–72)	<0.01*
Male (%)	15 (65)	15 (88)	0.09**
CCI, (range)	2.23 (0–8)	2.11 (0–3)	0.76*
Age adjusted CCI, (range)	3.29 (0–10)	3.95 (1–6)	0.21*
Mean tumor # (range)	6.2 (1–25)	4.3 (1–11)	0.21*
Procedure per patient (range)	2.3 (2–6)	2.6 (2–3)	0.67*
Histologic concordance (%)	9/23 (39)	16/17 (94)	<0.01**

* student T-test

** Fisher's Exact test