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ANATOMICAL PATHOLOGY

Renal oncocytosis: a clinicopathological and cytogenetic study of 42 tumours occurring in 11 patients

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Summary

Renal oncocytosis is a rare pathological condition characterised by the presence of multiple oncocytic tumours with a spectrum of histological features ranging from renal oncocytoma, hybrid oncocytic tumour and rarely chromophobe renal cell carcinoma, sometimes overlapping. Here we retrospectively analysed histological, immunohistochemical (IHC), and cytogenetic features of 42 lesions in 11 patients with renal oncocytosis, not associated with Birt–Hogg–Dubé syndrome. The histology of all the lesions was blindly reviewed by three dedicated genitourinary pathologists. IHC for cytokeratin 7 (CK7) and fluorescence *in situ* hybridisation (FISH) for copy number variation of chromosomes 1, 6, 7 and 17 were performed in all 42 nodules. Among the 42 lesions 36 (85.7%) were histologically renal oncocytomas, two (4.76%) 'hybrid oncocytic tumours' (HOT), one (2.4%) clear cell renal cell carcinoma (ccRCC), one (2.4%) papillary renal cell carcinoma (pRCC), one typical angiomyolipoma (2.4%), and one mixed epithelial/stromal tumour of the kidney (2.4%). FISH analysis confirmed the histological diagnosis of all the lesions. We show that most patients with renal oncocytosis harbour benign or low malignant potential tumours that can be treated conservatively.

Key words: Renal oncocytosis; hybrid tumours; oncocytoma; kidney.

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INTRODUCTION

Renal oncocytoma (RO) is an epithelial lesion that accounts for 3–7% of all adult renal epithelial neoplasms and most commonly affects males in the seventh decade of life. RO is by definition a benign tumour according to the literature, with no patients dying of this disease and only two patients reported to bear possible metastases.[1] ROs are typically single, well-defined, non-encapsulated lesions. In rare instances, ROs may present as multifocal and bilateral, and in this setting the disease is named renal oncocytosis.[2] Renal oncocytosis is an infrequent pathological condition characterised by the presence of multiple and/or bilateral oncocytic tumours with a spectrum of histological changes ranging from renal RO to chromophobe renal cell carcinoma (ChRCC). In addition, the association of RO with other histotypes of renal cell cancer can be found in 10–32% of renal oncocytosis with unilateral or bilateral tumour localisation.[2]

A common finding in renal oncocytosis is the occurrence of 'hybrid' oncocytic tumours with intermediate morphological features between RO and ChRCC. Many hypotheses have been offered in past years about the relationships among RO, ChRCC and 'hybrid oncocytic tumour' (HOT). Since the three lesions frequently occur in the context of renal oncocytosis, this pathological condition has often been used as a model for understanding the biological background of oncocytic tumours and their possible interconnections. Some authors have suggested that a spectrum of oncocytic lesions may exist, evolving from RO throught HOT and finally to ChRCC. This hypothesis is supported by data on specific chromosome losses shared by HOT and ChRCC such as loss of chromosomes 14 and 21.[3] Other authors have suggested that HOT is not related to ChRCC, but rather represents the evolution of RO following the occurrence of additional chromosome aberrations, and that HOT and ChRCC actually derive from RO as a common precursor lesion.[3] Finally, according to another hypothesis, all of these tumours represent independent entities, both phenotypically and genotypically.[4] The most recent classification of renal tumours proposed by the International Society of Urological Pathology (ISUP) in 2013 supports this latter hypothesis and introduced hybrid oncocytic tumours as a separate entity. Therefore, according to this recent classification of renal tumours, renal oncocytosis-related HOTs should be considered distinct tumours and not intermediate steps of the morphological progression from renal oncocytosis to ChRCC.[5]

From the clinical standpoint, HOTs may occur in three different clinicopathological settings: sporadic, in association with renal oncocytosis, or in carriers of the Birt–Hogg–Dubé (BHD) syndrome, a rare autosomal inherited dominant disease characterised by skin lesions (fibrofolliculomas of the face and head and neck), pulmonary cysts and renal neoplasms.[6] Tumours occurring in the three above conditions

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share similar morphological features also common to RO and ChRCC.[4,7–9] However, the different molecular characteristics of each lesion are still not completely defined.

Here, we provide a histological, immunohistochemical (IHC) and cytogenetic analysis of 42 different lesions from 11 patients with renal oncocytosis not associated with BHD syndrome.

MATERIALS AND METHODS

We retrospectively evaluated 42 kidney lesions from 11 patients with renal oncocytosis diagnosed from 2009 to 2013 in the pathology divisions at the S.Orsola-Malpighi Hospital (Bologna, Italy) and the San Luigi Hospital (Orbassano, Turin, Italy). We aimed to analyse any lesion that was removed from each patient to confirm their histological, immunohistochemical and cytogenetic features. Renal oncocytosis was defined as the presence of at least two oncocytomas either in the same kidney or bilaterally.

The mean age of the patients at nephrectomy was 63.8 ± 15.97 years (range 41–85), six (54.5%) patients were males and five (45.5%) females. Twenty-five (60.9%) lesions were in the left kidney and 16 (39%) in the right kidney. Five patients (45.5%) underwent laparoscopic radical or partial nephrectomy.

The majority (10/11) of the patients were asymptomatic at the time of the diagnosis and the detection of renal masses has been incidental during abdominal ultrasound performed for other clinical reasons or routine check-up. One case presented with haematuria (Table 1).

All lesions were histologically reviewed by three dedicated uropathologists, blinded to the original pathology report, and classified according to the 2013 ISUP classification.[5] Surgical specimens were formalin fixed, paraffin embedded and routinely processed for histological diagnosis. Three µm thick sections were cut from paraffin blocks and stained with haematoxylin and eosin and 4 µm thick sections were prepared from blocks comprehensive of normal renal tissue and neoplastic tissue for IHC and fluorescent *in situ* hybridisation (FISH) analyses.

Immunohistochemical analysis

IHC for cytokeratin 7 (SP52, prediluted; Ventana Medical Systems, USA) and alpha methyl CoA racemase (P504S, 1:100; Ventana Medical Systems) was performed in all cases using an automated Benchmark Ultra instrument (Ventana Medical Systems).

We performed IHC for CK7 for the differential diagnosis among oncocytic lesions according to the recommendations of the ISUP.[5]

Immunoreativity for CK7 was scored as negative when only single scattered tumour cells or entrapped native renal tubules were stained; intermediate when the immunoreactivity was limited to clusters of tumour cells; and positive when the tumours were strongly and diffusely positive for CK7.

Table 1 Clinical features

Patient	Sex	Age	Side	Surgery	Symptoms	Follow-up (months)
1	M	77	L	NSN	Asymptomatic	NED (20)
			R	NSN		
2	F	50	R	NSN	Asymptomatic	NED (20)
3	M	41	R	NSN	Asymptomatic	RD (17)
4	M	60	L	RN	Asymptomatic	NED (24)
5	M	68	L	NSN	Asymptomatic	NED (5)
6	M	45	L	NSN	Asymptomatic	NED (36)
			R	NSN		
7	F	67	L	RN	Asymptomatic	NED (36)
			R	NSN		
8	F	48	L	NSN	Asymptomatic	NED (24)
			R	NSN		
9	M	85	R	NSN	Haematuria	NED (12)
			L	NSN		
10	F	78	L	RN	Asymptomatic	NED (3)
11	F	83	R	NSN	Asymptomatic	NED (3)

F, female; L, left; M, male; NED, no evidence of disease; NSN, nephron-sparing nephrectomy; R, right; RD, recurrent disease; RN, radical nephrectomy.

FISH analysis

FISH analyses were performed using: (1) the ZytoLight SPEC VHL/CEN3 Dual Color Probe (ZytoVision, Germany) to detect chromosome 3p status; (2) centromeric DNA probes for chromosome 1 (CEP 1, Spectrum Orange), chromosome 6 (CEP 6, Spectrum Green), chromosome 7 (CEP 7, Spectrum Green), and chromosome 17 (CEP 17, Spectrum Orange; all CEP probes from Abbott Molecular, USA), to detect chromosomes losses/gains.

Briefly, slides were baked at 60°C overnight, deparaffinised, pretreated at 98°C for 15 min in citric acid solution (PT1; ZytoVision) and digested with pepsin solution (ES1; ZytoVision) at 37°C for 8 min. Co-denaturation and hybridisation were performed on an automated ThermoBrite (Abbott Molecular) at the following conditions: (1) 75°C for 10 min and 37°C overnight, for VHL/CEP3 probes; (2) 85°C for 2 min and 42°C overnight for CEP1/CEP 6 and CEP7/17 probes. After two washes in 2XSSC/0.3%NP40, at room temperature for 2 min and at 73°C for 2 min, slides were air-dried and counterstained with DAPI I (4′-6'-diamidino-2-phenylindole dihydrochloride hydrate) antifade solution (Abbott Molecular).

Slides were evaluated with an epi-fluorescence microscope (Nikon Eclipse 80; Nikon Corporation, Japan) equipped with single band-pass filters. For each sample, 80–100 neoplastic nuclei were analysed under high-power magnification (1000×), and non-neoplastic kidney parenchyma was scored as well and used as control.

The cut-off values for the definition of chromosomal gains and losses were set at the mean ±3 SD of the control values (non-neoplastic cells). Any tumour with a signal score beyond the cut-off value was considered to have gain or loss of that chromosome.

RESULTS

Clinical, histological and molecular characteristics of all the lesions are described in Tables 1 and 2. Mean tumour size was 2.8 ± 2.01 (range 0.6–9.0). Histological review of the cases was concordant among the three dedicated genito-urinary pathologists and the 42 lesions were classified as follows: 36/42 (85.7%) oncocytoma, two (4.76%) hybrid oncocytic tumour, one (2.4%) clear cell carcinoma, one (2.4%) papillary renal cell carcinoma (pRCC), one typical angiomyolipoma (2.4%), and one mixed epithelial/stromal tumour of the kidney (2.4%) (Table 2).

Oncocytomas

All the ROs in the series had typical gross features: well circumscribed nodules with a mahogany-brown cut surface. Histologically, they displayed a solid growth pattern, small clusters of tubule-like structures and nests of large round to polygonal cells with granular eosinophilic cytoplasm, round nuclei and central single nucleoli. No necrosis or atypical mitoses were observed. Two cases presented with an additional infiltrative pattern of the perinephric adipose tissue.

IHC for CK7 was negative in all of these lesions (Fig. 1A,B). FISH analysis confirmed the histological diagnosis of RO with a diploid status for chromosomes 6 in all the lesions and loss of chromosome 1 in just five of 29 tumours (Fig. 2A–C).

Two oncocytomas in Patient 6 were otherwise histologically typical except for the presence along the central fibrous scars of tubulo-papillary structures with an infiltrating pattern and apparently interconnected with the main oncocytic lesion. Unlike the oncocytic counterpart, these cells arranged in the tubulo-papillary structures were strongly immunoreactive for AMACR and CK7 (Fig. 1E,F). The FISH analysis confirmed that the oncocytic lesion was diploid for chromosomes 1, 6, 7 and 17, while the tubulo-papillary structures showed the gain of chromosome 17, typical of pRCC (Fig. 2C,D). The other four lesions from the same patient were conventional 'pure' RO at histological, IHC and FISH analysis.