Abstract. The clinical and pathological features of multiple different renal neoplasms arising in a setting of end-stage renal disease in a 72-year-old male are described. The kidney showed features of renal oncocytosis with multiple oncocytomas, hybrid tumours and chromophobe renal carcinoma. In addition, the kidney contained a type 2 papillary renal cell carcinoma, clear cell papillary and cystic renal cell carcinoma, and tubulocystic carcinoma. The occurrence of these three tumours in a setting of end-stage kidney disease is unique and suggests a common pathogenesis. Immunostaining of these tumours further suggests they are derived from similar stem cells which show immunophenotypic features of both the proximal and distal nephron.

The Rochester/Heidelberg consensus conferences held in 1996 and 1997 provided the foundation for the detailed classification of renal parenchymal neoplasia (1, 2). In addition, these classifications acted as a framework for the identification of further tumour variants, and over the past thirteen years, a number of novel forms of renal neoplasia have been described (3). Parallel with the identification of unique morphotypes of renal neoplasia, attempts have been made through genetic and antigen marker studies to elucidate any possible relationship between these newly described tumour types.

Clear cell renal cell carcinoma (RCC), papillary RCC and chromophobe renal carcinoma are the three most frequently encountered forms of renal parenchymal malignancy and each of these have been shown to be associated with unique genetic abnormalities (1). The relationship of the newly described entities of renal carcinoma to these tumours is less certain and in particular that of tubulocystic carcinoma and clear cell papillary and cystic RCC, to typical papillary RCC is unclear. In some studies, it has been suggested that tubulocystic carcinoma and papillary RCC show some similarities to each other in both genetic changes and immunoexpression (3, 4).

We present a unique case of renal oncocytosis with chromophobe renal carcinoma, oncocytoma and hybrid tumours, with co-existing papillary RCC, clear cell papillary and cystic RCC, and tubulocystic carcinoma. The occurrence of varieties of papillary RCC and tubulocystic carcinoma in a background of renal oncocytosis and end-stage renal disease provides further evidence of an inter-relationship between these tumour types.

Case Report

A 72-year-old male, with a history of chronic renal failure of unknown aetiology, underwent investigation of elevated liver enzymes. Renal ultrasound showed a solid mass 3.1 x 3.6 cm in the mid-pole of the left kidney with two small simple cysts. Subsequent magnetic resonance angiography confirmed this and showed three further solid tumours in the left anterior mid-pole, mid-portion and lower pole of the right kidney measuring 1.8 cm, 1.9 cm and 1.3 cm in diameter respectively. A cystic structure 2.6 cm in maximum extent was also present in the left upper pole. The patient underwent left radical nephrectomy.

The surgical specimen was sampled extensively and blocks were taken from all macroscopically visible lesions,
as well as from apparently normal renal cortex and medulla. Sections were stained with haematoxylin and eosin. In addition, immunohistochemical stains were undertaken on the tumours using antibodies to cytokeratin 7 (CK 7), CD 10, racemase (AMACR), 34βE12 and CK 20 (Dako Corporation, Carpinteria, CA, USA).

In the gross specimen, a large cyst in the upper pole and a haemorrhagic tumour in the mid-portion of the kidney, as well as multiple small tumours within the cortex and medulla, were visible macroscopically (Figure 1).

Histological examination showed the left kidney to contain both benign and malignant tumours. The large tumour noted on imaging studies was an oncocytoma. Six further oncocytomas were identified. In the upper pole there was a chromophobe renal carcinoma measuring 10 mm in diameter. Two further oncocytic tumours had features of both oncocytoma and chromophobe renal carcinoma consistent with so-called hybrid tumours. These tumours were well circumscribed without evidence of direct infiltration into renal tissue. In these tumours, there was focal nuclear pleomorphism with perinuclear clearing. These changes were only seen in small groups of cells, and the remainder of both tumours showed features typical of oncocytoma. Oncocytic change was also present within non-neoplastic tubular epithelium in areas distant from oncocytomas, hybrid tumours and the chromophobe renal carcinoma.

Three further tumours were also identified. One of these was a compact type 2 papillary RCC (Figure 2). This was situated in the lower pole of the kidney and measured 10 mm in diameter. This tumour was invested by a pronounced pseudocapsule and had nuclear features consistent with grade 2 of Fuhrman’s nucleolar criteria (5, 6). The second tumour was a clear cell papillary and cystic RCC (Figure 3). The tumour was predominantly cystic, with cysts lined by clear cells exhibiting minimal nuclear pleomorphism without visible nucleoli. Within the cysts, there were papillary projections with papillae covered by clear cells. The third tumour was present in the lower pole and measured 10 mm in diameter. This consisted of sheets containing epithelium-lined tubules with scant fibrovascular stroma. The tumour cells showed moderate nuclear pleomorphism with small nucleoli and eosinophilic cytoplasm (Figure 4) consistent with a diagnosis of tubulocystic carcinoma.

The immunohistochemical expression of the tumours is shown in Table I.

Discussion

The presence of oncocytomas, hybrid tumours and chromophobe renal carcinoma, with oncocytic change in benign tubules is diagnostic of renal oncocytosis (7). This is a diffuse neoplastic process that involves both kidneys and the identification of multiple tumours on imaging of the right kidney in our case supports this diagnosis. Renal oncocytosis
may occur sporadically, but is occasionally found in association with the Birt–Hogg–Dubé syndrome (8). The patient did not have the cutaneous features of the syndrome and his oncocytosis was considered to be the sporadic form.

In addition to the multiple tumours of oncocytosis, the kidney also contained three separate renal parenchymal tumours: papillary RCC, clear cell papillary and cystic RCC, and tubulocystic carcinoma.

Papillary RCC is the second most common form of RCC, and is often associated with renal scarring and end-stage renal disease (9, 10). These tumours are genetically heterogeneous, although trisomy of chromosomes 7 and 17 and loss of Y chromosome is commonly seen. Occasionally these tumours occur in association with mutations in the MET oncogene as hereditary papillary RCC; however, unlike the tumour in the present case, these tumours show type 1 morphology (11).

Clear cell papillary and cystic RCC is an emerging form of RCC and was originally described as one of the two novel types of renal neoplasia associated with end-stage renal disease (12). Recently, tumours of similar morphology have been also found in otherwise normal kidneys (13). The genetic mutations associated with these tumours are yet to be fully elucidated, although fluorescence in situ hybridisation (FISH) studies on two sporadic tumours showed gains of chromosome 17. In the few cases studied to date, both sporadic and end-stage renal disease-related tumours showed positive expression for cytokeratin 7, focal expression of CD 10 and negative staining for racemase (12, 13), as was seen in our case.

Tubulocystic carcinoma is a newly recognised type of renal neoplasia that was originally considered to be low-grade collecting duct carcinoma (14). In reality, these tumours are neither low grade nor of collecting duct origin and have been shown to be associated with trisomy of chromosomes 7 and 17 (15). These tumours have been previously found in association with typical papillary RCC and in a small series of cases, 23% of patients with tubulocystic carcinomas also had papillary RCC in the same kidney (4). Ultrastructurally, tubulocystic carcinoma cells have brush borders suggestive of

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<th>Table I. Immunohistochemical staining of tumours.</th>
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<td>CK 7</td>
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<td>Oncocytoma</td>
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<td>Hybrid tumour</td>
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<td>Chromophobe renal carcinoma</td>
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<td>Type 2 papillary renal cell carcinoma</td>
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<td>Clear cell papillary and cystic renal cell carcinoma</td>
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<td>Tubulocystic carcinoma</td>
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N, Negative, lack of staining; F, focal staining; D, diffuse staining; +, weak; ++, moderate; ++++, strong staining.
an origin from proximal convoluted tubule cells (16). Positive immunoexpression for the proximal nephron markers, AMACR and CD 10 has been reported for tubulocystic carcinoma (15). It has also been shown that these tumours exhibit positive expression of CK 7, which is usually associated with cells of the distal nephron (3). In our case, the tubulocystic carcinoma showed diffuse, positive staining for all three markers.

In the present case, the patient has features of renal oncocytosis and clinical evidence of impaired renal function. In this background of tumour-associated end-stage renal disease, three separate tumours had developed. The occurrence of these three tumours in a single kidney has not been previously reported and this association would seem to provide evidence that these morphotypes are related, in terms of pathogenesis. All of these tumours exhibited a tubulopapillary/papillary architecture and showed common expression of CK 7, an immunomarker associated with the distal nephron, as well as positive expression of proximal nephron markers. This similar immunoexpression is consistent with a similar cell of origin for these three tumour types and the expression of both proximal and distal nephron markers suggests that these may be derived from renal tubule stem cells.

References


Received September 2, 2009
Revised January 27, 2010
Accepted January 29, 2010