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Renal Oncocytoma

A Review of the Literature and Report of an Unusual Multicentric Case

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Summary. Renal oncocytoma is a rare tumour of the kidney composed exclusively of large polygonal cells with eosinophilic, granular cytoplasm. Ultrastructurally they are distinguished by the presence of large numbers of mitochondria and histochemically by abundant oxydative enzymes and adenosine triphosphate. Macroscopically these tumours are usually light brown in colour and commonly exhibit a dense central area of fibrous scarring, with fibrous trabeculae extending from this central zone in a stellate fashion. Renal oncocytomas are commoner in males than females (sex ratio 2:1) and although the age range at presentation is wide, there is a peak incidence in the seventh decade. The prognosis following surgical removal is excellent, despite the fact that many of these tumours are large. Invasion of the perirenal fat and the renal vein and metastatic spread to regional lymph nodes is documented, but death from metastatic disease is rare. The great majority of renal oncocytomas reported are solitary. We describe a multicentric renal oncocytoma, the sixth so far reported.

Key words: Renal Neoplasm – Oncocytoma – Eosinophilic adenoma

Recently the renal oncocytoma, a rare tumour which may reach huge size without producing metastases, has been put forward as a new candidate for the long disputed title of "benign adenoma" of the kidney. Following isolated reports in the world literature Klein and Valensi (1976) published the first comprehensive account in the English language literature of what they termed "proximal tubular adenoma of the kidney with so-called oncocytic features". Since then numerous further case reports have appeared in the world literature (Table 1). Despite the fact that most reports document distinctive gross, microscopic, ultra-structural and angiographic features and

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an exceptionally good prognosis, some authors (Jander 1979) still question the existence of the renal oncocytoma as a separate entity. It is with this continued uncertainty in mind that we have reviewed the world literature, in order to define more clearly the presentation, behavior and treatment of this uncommon neoplasm. In addition, we present an unusual, multicentric case.

Table 1. A summary of the world literature

Reference source	No. of cases	No. of males	No. of females	Age range (years)	Size range (cm)	Presentation			Follow up period (Years)
						Symptomatic	Incidental finding	Autopsy finding	
Zippel (1942)	1	1	0	57	NS	0	0	1	–
Zollinger (1969)	1	1	0	58	10	NS	NS	NS	3
Wasilkowski and Dabrowski (1971)	1	0	1	41	18	1	0	0	NS
Berger et al. (1973)	1	0	1	41	Multicentric	0	1	0	Recent
Blessing and Wienert (1973)	1	0	1	47	19	1	0	0	0
Duclos et al. (1975)	4	4	0	22–63	NS	2	2	0	NS, 3, 11
Sos et al. (1976)	4	4	0	54–62	1–5	0	4	0	3, 3, 7, 9
Klein and Valensi (1976)	14	9	5	48–80	3.5–13	0	14	0	1–11, mean = 4.8
Milstoc (1977)	1	1	0	93	5	0	0	1	–
Weiner and Bernstein (1977)	2	2	0	35, 79	9, 10.6	1	1	0	Recent
Rothenberger et al. (1978)	1	1	0	69	12	1	0	0	1
Marek et al. (1979)	7	5	2	51–80	5–26	NS	NS	4	2, 7, 17
Pearse (1979)	1	1	0	15	NS	0	1	0	1
Wojtowicz et al. (1979)	1	1	0	38	13	1	0	0	NS
Weedon et al. (1979)	1	0	1	51	14	0	1	0	NS
Johnson et al. (1979)	2	2	0	49, 82	7, 10	0	2	0	NS

Table 1 (continued)

Reference source	No. of cases	No. of males	No. of females	Age range (years)	Size range (cm)	Presentation			Follow up period (Years)
						Symptomatic	Incidental finding	Autopsy finding	
Ejeckham et al. (1979)	8	5	3	30–84	2.5–10	3	2	3	Recent, 5, 6
Landier et al. (1979)	8	5	3	38–69	3.5–16	5	3	0	2–9, mean = 5.5
Chaudhry et al. (1979)	1	0	1	85	12	0	1	0	NS
Akhtar and Kott (1979)	2	0	2	50, 77	9, 11	0	2	0	1, 6
Kay and Armstrong (1980)	3	3	0	42–58	2.3–10.6	1	2	0	Recent, 28
Morales et al. (1980)	4	3	1	40–70	1–11.5	2	1	1	2, 7, 8
Yu et al. (1980)	5	5	0	53–79	5–10.6	1	4	0	2, 2, 11, 11, 13
Schmidt and Taenzer (1980)	1	1	0	70	2.5	0	1	0	NS
Rodriguez et al. (1980)	1	1	0	76	Multicentric	0	1	0	1
Kendall et al. (1980)	1	1	0	67	5	0	1	0	NS
Bono et al. (1980)	1	1	0	57	6	0	1	0	Recent
Barth and Menon (1980)	2	1	1	34–62	10–15	0	2	0	NS
Lautin et al. (1981)	4	4	0	63–78	5.5, 7.5, 2 × multicentric.	1	3	0	NS
Bonavita et al. (1981)	14	7	7	41–77	2.5–13 Mean = 5.0	NS	NS	0	NS
Bokinsky (1981)	1	0	1	37	15	0	1	0	NS
Lieber et al. (1981)	90	57	33	29–84	3–26	37	53	0	up to 30
Harrison et al. (1981)	1	0	1	62	6	1	0	0	10
Wolf et al. (1981)	1	0	1	37	12	1	0	0	2
Woodard et al. (1981)	1	1	0	74	Multicentric	0	1	0	NS

Table 1 (continued)

Reference source	No. of cases	No. of males	No. of females	Age range (years)	Size range (cm)	Presentation			Follow up period (years)
						Symptomatic	Incidental finding	Autopsy finding	
Susman et al. (1981)	1	1	0	72	NS	1	0	0	1
Moura and Nascimento (1982)	1	0	1	34	Bilateral	1	0	0	6
Warfel and Eble (1982)	1	0	1	71	"Oncocytomatosis"	0	0	1	–
Present case	1	1	0	74	Multicentric	0	1	0	2
Totals	196	129 (66%)	67 (34%)	15–93 Median = 61.1[a]	1–26 Median = 6.9[b]	60	106	11	–

[a] 166 clinically discovered cases in which the age was stated
[b] 142 clinically discovered cases in which the size was stated

Abbreviations: NS = Not stated

Case Report

Clinical Data. A 74 year old white male was admitted to hospital after having collapsed at home. He had been feeling vaguely unwell for the previous 2–3 days and had noticed some urinary frequency. He was pyrexial (38° C) and bacteriological examination of the urine revealed an E. coli urinary tract infection. He had no symptoms of loin pain or haematuria and responded well to treatment with antibiotics. An excretory urogram revealed a mass in the lower pole of the left kidney. Ultrasonography showed a solid lesion in the same site and a renal arteriogram was reported as showing a carcinoma of the left kidney. Further careful examination of the abdomen revealed that there was a palpable left renal mass. A left radical nephrectomy and splenectomy were performed. No evidence of metastatic spread was found. After an uneventful convalescence he was discharged home and remains well 2 years later.

Pathology. The left radical nephrectomy specimen weighed 403 g. Removal of the peri-nephric fat revealed an ovoid tumour measuring $8 \times 7.5 \times 7$ cm protruding from the lateral border of the kidney (Fig. 1). A second tumour measuring $2.5 \times 2.5 \times 2.2$ cm protruded from the lower pole and a 4.5 cm diameter, thin-walled, cortical cyst was present in the upper pole. Cross-sectioning the kidney revealed a third tumour measuring $1.8 \times 1.1 \times 1.1$ cm in the medial wall of the cortical cyst. The largest tumour was sharply demarcated from the renal parenchyma but poorly encapsulated. Small tongues of tumour penetrated up to 0.4 cm through the renal capsule into the perinephric fat, but satellite nodules were not present. The cut surface varied from tan to dark brown in colour. Myxoid areas were prominent and haemorrhage into these had produced the darker coloured areas. Small cysts 0.1–0.4 cm in diameter were scattered diffusely through the tumour. Delicate strands of fibrous tissue traversed the tumour in a stellate fashion. Although the lower pole tumour was also sharply demarcated, a blunt tongue of tumour protruded into the renal parenchyma but the overlying renal capsule was intact.

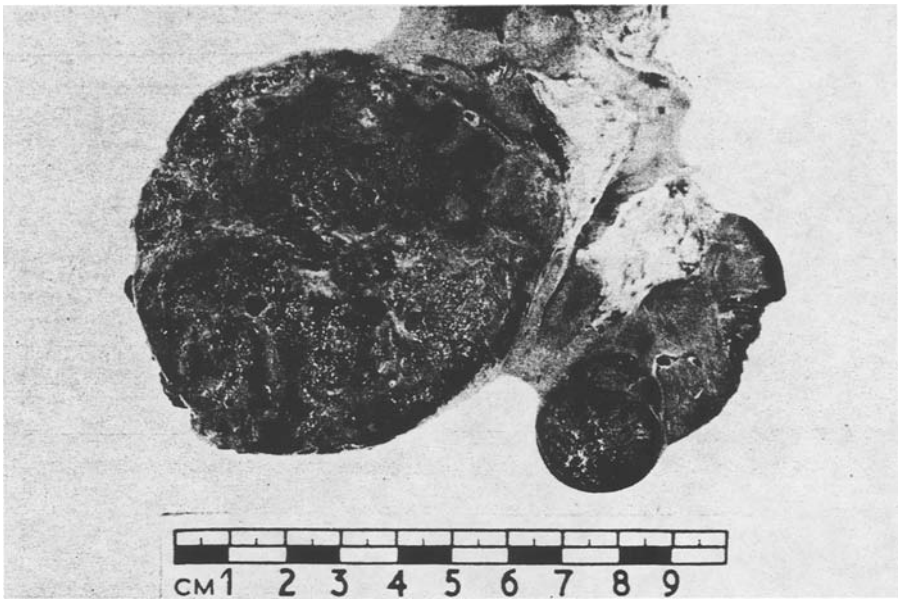

Fig. 1. Left nephrectomy specimen showing two separate oncocytomas. The 3rd tumour nodule protruded into a cortical cyst. Note numerous microcysts and protrusion of smaller tumour into renal parenchyma

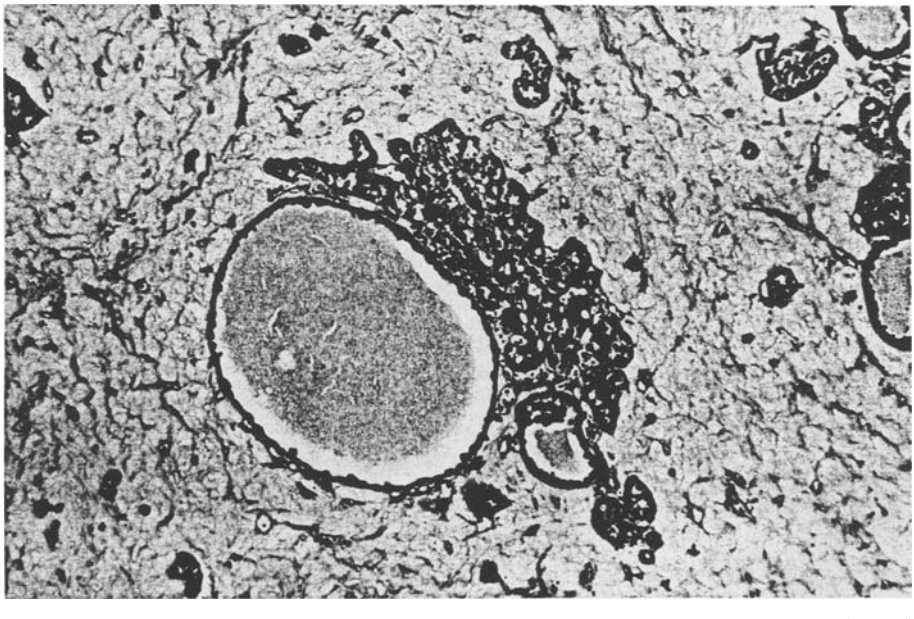

Fig. 2. Low power photomicrograph showing oncocytic tubules lying within the myxoid matrix. (H and E, × 70)

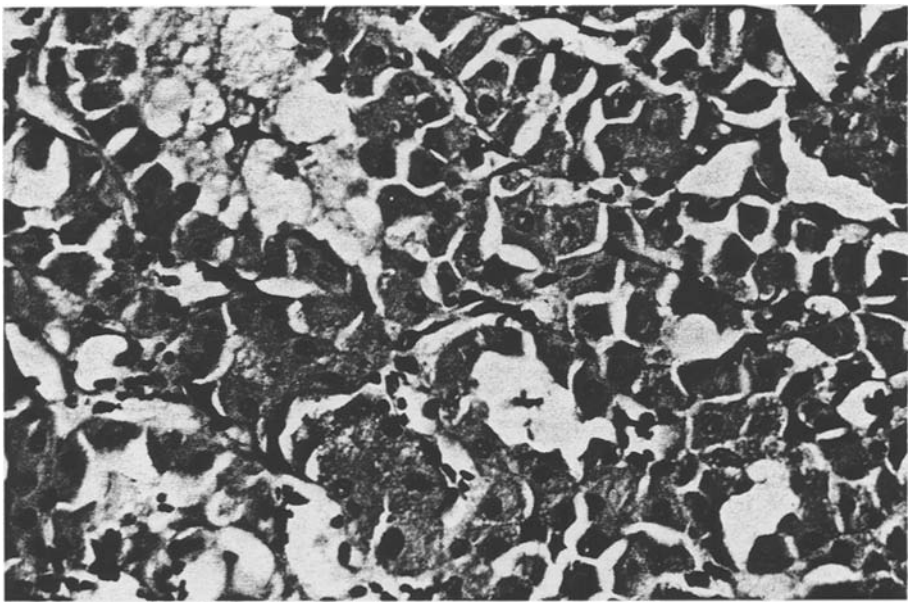

Fig. 3. High power photomicrograph of a more solid area of the tumour showing typical plump oncocytes with round regular nuclei and granular cytoplasm. The separation of the cells is typical fixation artifact. (H and E, × 400)

The smallest tumour jutted into the cortical cyst and was sharply circumscribed. The cut surfaces of both smaller tumours were similar to the largest, but haemorrhage was less marked. There was no evidence of invasion of the renal vein or of metastatic spread to regional lymph nodes.

Microscopically all three tumours are similar in appearances and are composed of oncocytes arranged in nests, strands, tubules and occasional cystic structures lying in a myxoid matrix (Fig. 2). Areas of recent haemorrhage, both into the myxoid stroma and into the tubules are conspicuous and haemosiderin is present in some areas. The tumours are separated from the renal parenchyma by a thick band of compressed fibrous tissue containing numerous muscular arteries. Muscular arteries are also present in the peripheral parts of the tumours but are much less frequent and of smaller calibre in the centres of the tumours. Small vessels lacking a muscular wall are present throughout the tumours.

The oncocytes are typically plump cuboidal cells with a strongly eosinophilic, coarsely granular cytoplasm (Fig. 3). The nuclei are small, with coarse, regularly arranged chromatin and occasional nucleoli. Pleomorphism and mitoses are absent. There is no evidence of invasion into vessels.

Immunohistochemically, staining of paraffin-embedded sections of the tumour by the unlabelled antibody HRP-anti-HRP (PAP) method (Sternberger et al. 1970) using rabbit anti-human Tam Horsfall protein is uniformly negative.

Ultrastructurally the tightly packed polyhedral cells are characterized by large numbers of round to oval mitochondria and a paucity of other cytoplasmic organelles (Fig. 4). A basement membrane is present on one side of some of the cells. Occasional small desmosomes are present but microvilli, infoldings and other membrane specializations are absent.

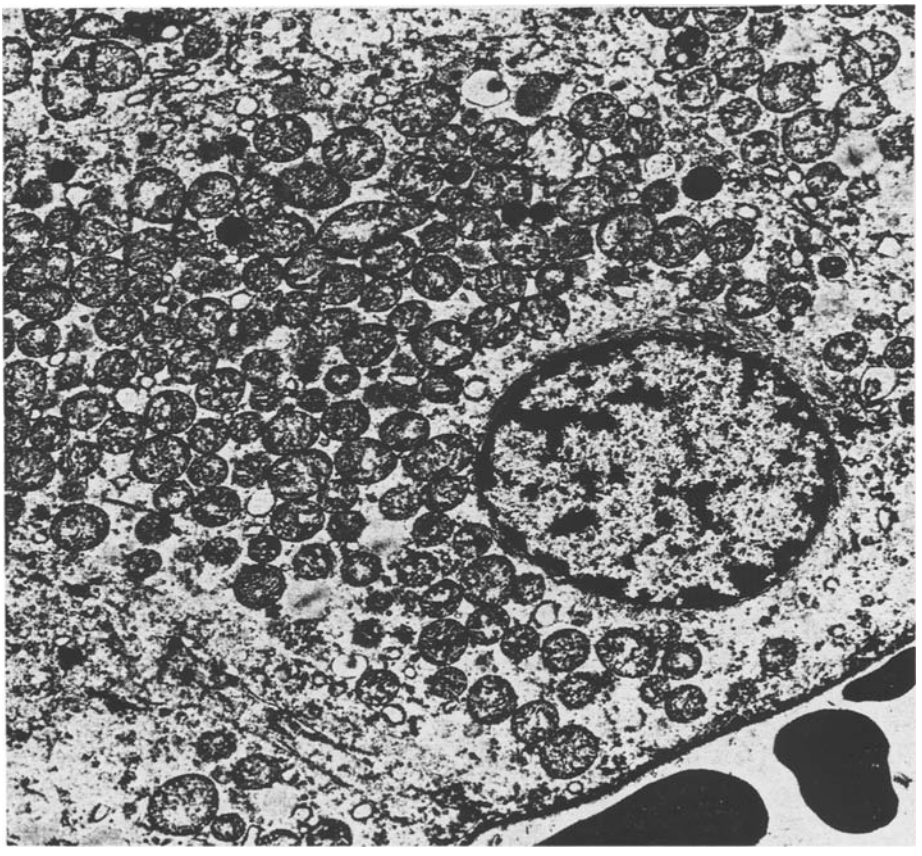

Fig. 4. Electron micrograph prepared from formalin fixed material, showing abundance of mitochondria and paucity of other cytoplasmic organelles. Note also the basement membrane and occasional desmosomes. (× 7,300)

Discussion

Table 1 summarizes 196 cases of renal oncocytoma reported in the world literature since 1942. We have excluded the report by Poroshin and Galyl-Ogly (1965) in the Russian literature and also that of Blessing et al. (1979), because the authors describe an oncocytoma intermingled with a "fibrous sarcoma" and this does not fulfill the criteria for a pure oncocytoma. Renal oncocytomas are also discussed by Apitz (1944) and Hamperl (1962) but the clinical and pathological details are not given in sufficient detail for inclusion. In addition, Riopelle (1951) included an oncocytoma in the series of tumours he termed "true kidney hypernephromas".

The incidence of renal oncocytomas (quoted as a percentage of renal carcinomas) is variously given as 1.3% (Bonavita et al. 1981), 3.2% (Lieber et al. 1981), 4% (Akhtar and Kott 1979), 4.4% (Ejeckham et al. 1979), 4.7% (Yu et al. 1980) and 6.7% (Klein and Valensi 1976). Bonavita et al. (1981) and Lieber et al. (1981) did not review the histology of carcinomas

not classified as oncocytomas and their figures may consequently be falsely low. The true incidence is probably around 4–5%. Klein and Valensi (1976) suggested that the incidence might be on the increase but Yu et al. (1980) and Lieber et al. (1981) found no evidence of this. Including autopsy cases, the male:female ratio is 1.9:1. Of the 166 cases in which clinical information is available, 64% of tumours were discovered incidentally and 36% were symptomatic. Of these, flank pain was present in 71%, haematuria in 33%, weight loss in 7% and fever in 8%. A non embolic systemic vasculitis which disappeared after removal of a renal oncocytoma is described by Susman et al. (1981). The age range at clinical presentation is wide (Table 1) with peak incidence in the 7th decade. Some very large solitary tumours have been described (Table 1), 25.4% measuring greater than 10 cm in diameter at clinical presentation. Multicentric oncocytomas occur rarely (Berger et al. 1973; Rodrigues et al. 1980; Lautin et al. 1981; Woodard et al. 1981). Usually 2 or 3 tumours measuring between 2.5 and 8 cm are found but several small nodules may also be present. Warfel and Eble (1981) report a case in which over 200 oncocytomas measuring up to 1.2 cm in diameter were present in both kidneys and coin the term "renal oncocytomatosis" to describe this phenomenon. Moura and Nascimento (1982) describe a case of bilateral renal oncocytomas. The patient refused surgery and was well 6 years after initial diagnosis.

Macroscopically the typical renal oncocytoma is a well circumscribed, partially to totally encapsulated round to ovoid tumour which on cross section is tan to mahogany in colour, probably related in part to the large quantity of cytochrome pigments in the numerous mitochondria. Areas of haemorrhage (Weedon et al. 1979; Ejeckam et al. 1979) and necrosis (Weiner and Bernstein 1977) have been described but are uncommon. Myxoid (Morales et al. 1980) and cystic areas (Ejeckam et al. 1979; Akhtar and Kott 1979) occasionally occur. A very characteristic finding is a stellate fibrous tissue skeleton which may form a dense central fibrous scar. Fibrosis may be so marked as to produce a nodular irregular tumour with lobules divided by connective tissue septa (Chaudhry et al. 1979).

Microscopically the oncocytes may be arranged in a solid, trabecular, papillary or tubular pattern. The tubules may be solid or cystic and frequently contain eosinophilic proteinaceous material or blood. Brush borders are occasionally reported (Pearse and Houghton 1979). In the papillary forms, calcospherites have been recorded (Ejeckam et al. 1979). Mitoses are usually few in number. Pleomorphic nuclei and multinucleated cells are occasionally described. The stroma is characteristically vascular but varies from scanty to abundant with tubules widely separated by acellular myxoid areas. Haemorrhage may occur into these myxoid areas, probably due to inadequate support for the delicate vasculature. Histochemically the oncocytes are characterized by abundant oxydative enzymes and adenosine triphosphate (Hamperl 1962).

Ultrastructurally the oncocytes are characterized chiefly by the striking number of mitochondria. Free ribosomes, polyribosomes, rough endoplasmic reticulum and a Golgi apparatus are present but in small quantities.

Scanty particulate glycogen, lipid granules, coated and uncoated vesicles, membrane-bound dense lyzozomes and pinocytotic vesicles are also described. The mitochondria are usually round to ovoid and small in size, although they are described as large and swollen by Klein and Valensi (1976) and Kay and Armstrong (1980). The latter appearance may represent a fixation artifact. Varying numbers of tubular and vesicular cristae are present and the tubular cristae are sometimes arranged in parallel stacks in the center of the organelle (Chaudhry et al. 1979; Yu et al. 1980). Yu et al. (1980) noted dense osmiophilic granular aggregates within the mitochondrial matrix, supposedly representing ischaemic changes. Chaudhry et al. (1979) distinguished dark, intermediate and light oncocytes. Dark oncocytes are tightly packed with mitochondria and contain scanty other organelles. Light oncocytes are more loosely filled with mitochondria and contain a mixture of other cytoplasmic organelles. A basement membrane which may be invaginated is seen at the base of some cells. The cells are typically joined by small desmosomes. Chaudhry et al. (1979) described tight junctions, intermediate junctions and desmosomes in the apical, middle and basal parts of the cell interfaces. Luminal microvilli are usually present and Pearse and Houghton (1979) described a jumble of microvilli between adjacent cells.

The aetiology of oncocytic change is obscure. The subject has been extensively reviewed by Hamperl (1962), Tremblay (1969) and Sun et al. (1975). The use of the term "oncocytoma" has been rejected by Lennox (1948) and Klein and Valensi (1976). However, the authors find "oxyphilic adenoma", "mitochondrioma", and "adenoma with so-called oncocytic features" no more satisfactory. In the absence of a more acceptable alternative, the term "oncocytoma" usefully distinguishes a group of tumours of closely similar microscopic appearance occurring in a wide range of different organs, and does not have the connotations of benign behavior implicit in adenoma. The histogenesis of the renal oncocytoma remains controversial. Klein and Valensi (1976) noted the similarity under the light microscope between cells of the renal oncocytoma and proximal renal tubules. Their findings have been supported by Pearse and Houghton (1979) and Johnson et al. (1979). In our case and in those of Chaudhry et al. (1979) and Yu et al. (1980) microvilli were not found on electron microscopy, and this finding may support the histogenesis of at least some renal oncocytomas from the distal tubules. However Tandler et al. (1970) have noted that the loss of characteristic cytoarchitectural features is common to oncocytes in general, and Yu et al. (1980) feel that this lack of membrane specialization may only represent one of the stages of transformation of the oncocyte from its cell of origin, analogous to the well studied parathyroid oncocyte. Bannasch et al. (1978) have shown experimentally that oncocytomas may be induced in the rat kidney by nitrosomorpholine, and suggest an origin from the distal renal tubules but Eker et al. (1981) favour an origin in the proximal convoluted tubule. Tam-Horsfall protein is usually produced in the distal tubular cells, and in our case the failure of the oncocytes to stain positively with human Tam-Horsfall protein antisera may provide

further evidence against a distal tubular origin. However, the attenuation of cellular metabolism in oncocytes due to the proliferation of mitochondria may conceivably lead to loss of the ability to synthesize Tam-Horsfall protein, and negative staining cannot therefore be taken as conclusive evidence against a distal tubular origin. On balance, current evidence favours an origin from the proximal convoluted tubule.

Controversial claims have been made about the behavior of renal oncocytomas. Klein and Valensi (1976) found all their cases to be benign. However Hamperl (1962) had stated that he had observed 2 cases of malignant oncocytoma of the kidney, but gave no further details apart from 2 photomicrographs which show rather poorly differentiated tumours. Also Zollinger (1966) had illustrated a case of a microscopically typical oncocytoma of the kidney which had metastasized to bone 3 years after the nephrectomy. Following Klein and Valensi's article (1976), numerous reports appeared claiming benign behavior, based wholly on a failure to develop metastases, despite the fact that follow-up periods were often very short. However, Landier et al. (1979) recorded extension into the colon in a patient who died 3.5 years after surgery, apparently with venous and lymphatic spread. Akhtar and Kott (1979) and Rodriguez et al. (1980) described foci of tumour extension into perirenal adipose tissue. Both patients were alive and well 1 and 6 years after nephrectomy. Kay and Armstrong (1980) noted tumour emboli within thin-walled veins. There was no other evidence of invasion and the patient was apparently disease-free 7 months after nephrectomy. Lieber et al. (1981) studied a large series of 90 cases and found extension into the perirenal fat in 6, metastatic involvement of regional lymph nodes in 2, extension into the renal pelvis in 8 and involvement of the renal vein in 3 cases. Four patients died of metastatic tumour but the others were either alive and disease-free or had died of other causes. The patients were studied over a 29 year period and showed no excess mortality when compared with an age and sex matched cohort on a Kaplan-Meier actuarial survival curve. The histological nature of the distant metastases in the patients who died of their disease was not described but the tumour metastatic to lymph nodes was of oncocytic type. These cases show that oncocytomas of the kidney have proven ability to invade locally and metastasize to local lymph nodes and are almost certainly capable of metastasizing widely although in only a small percentage of cases. Clearly all future cases of malignant renal oncocytomas need to be carefully documented, with particular attention paid to the nature and site of metastases. Meanwhile, we propose that, in addition to actual metastases, all renal oncocytomas exhibiting the following characteristics should be regarded as at least potentially malignant: 1) Infiltration of perirenal tissues; 2) Invasion of the renal pelvis; 3) Growth of tumour in veins or lymphatics.

Renal oncocytomas have long been regarded as a separate entity by German Pathologists (Hamperl 1931 and 1962; Zippel 1942; Apitz 1944) but have only recently been recognized in the English language literature following Klein and Valensi's work in 1976. The many significant differences between renal oncocytomas and carcinomas are tabulated in Table 2. The closely similar microscopic appearances and biological behavior of oncocy-

Table 2. Comparison between renal carcinomas and oncytomas

	Carcinoma	Oncocytoma
Macroscopic		
Contour	Irregular, infiltrative	Smooth, encapsulated
Central scar	Uncommon	Common
Colour	Orange yellow to grey	Tan to mahogany
Necrosis and Haemorrhage	Common	Rare
Microscopic		
Cell types	Clear, granular and sarcomatoid	Monomorphous population of oncocytes
Ultrastructure	Clear cells contain plentiful cytoplasmic glycogen and lipid. Granular cells have fewer mitochondria than oncocytes, more cytoplasmic organelles, irregular nuclei and brush border lined intracytoplasmic lumina (Tannenbaum 1971)	Uniform cells with numerous mitochondria and few other cytoplasmic organelles
Angiographic		
Margination	Usually irregular	Sharp with "lucent" rim
Vascularization	Usually exuberant	Usually moderate
Regular or "spoke wheel" vascular pattern	Uncommon	Common
Homogeneous nephrogram	Uncommon	Common
Prognosis	Poor. Granular worse than clear cell. (Murphy and Mostofi (1965)	Excellent, even for large tumours

tomas in other organs, consistent with Hamperl's (1962) concept of convergent differentiation, lends further support to the existence of the renal oncocytoma as a separate entity. The salivary oncocytoma (oxyphilic adenoma), most frequently found in the parotid, may also be multicentric and bilateral (Lucas and Thackray 1978). Malignant behavior is unusual; Gray et al. (1976) accepted only 10 cases from the literature as being unequivocally malignant. Oncocytomas of the thyroid gland (oxyphil adenoma, Askanazy cell tumour, Hürthle cell tumour) are less rare. Bondeson et al. (1981) reviewed 42 cases of which 2 were multicentric and only 2 developed distant metastases. The clinical course of malignant thyroid oncocytomas is similar to that of follicular carcinomas (Tollefsen et al. 1975). Benign oncocytomas are described in the parathyroid glands (Roth et al. 1962) but malignant change has not been documented. In summary, the evidence for regarding the renal oncocytoma as a separate entity seems overwhelming.

The possibility of diagnosing oncocytomas pre-operatively has aroused considerable interest. The excretory urogram shows only a space-occupying lesion. Attention has centred largely around the angiographic appearances,

which have been described by Berger et al. (1973), Sos et al. (1976), Weiner and Bernstein (1977), Ambos et al. (1978) and Barth and Menon (1980). These are summarized in Table 2. Any renal tumour which on angiography has a regular or "spoke wheel" vascular pattern, a homogeneous nephrogram phase and is sharply marginated should be considered as a possible oncocytoma. However Older et al. (1978) found the combination unhelpful in pre-operative diagnosis and Ambos et al. (1978) and Jander (1979) reported the combination in 15% and 10% of renal carcinomas. Rodriguez et al. (1980) were able to diagnose an oncocytoma pre-operatively by aspiration cytology, obtained under ultrasonographic guidance. Large granular, eosinophilic oncocytes were easily distinguishable among smaller renal tubular cells. Experience with the use of fine needly aspiration techniques in "cold" nodules of the thyroid has shown that it is difficult to distinguish benign from malignant oncocytomas and even nodules occurring in autoimmune thyroiditis (Kini et al. 1981). Clearly, more experience is needed before this technique can be recommended without reservation. Wojtowicz et al. (1979) and Barth and Menon (1980) found computerized axial tomography unhelpful. Isotope scans have proved equally unsuccessful (Lautin et al. 1981). Intra-operative frozen section diagnosis has been used successfully by a number of authors (Pearse and Houghton 1979; Kay and Armstrong 1980; Bono et al. 1980). This procedure should present no great difficulties in diagnosis but it must be stressed that multiple sections are required before a pure oncocytoma can be diagnosed. The potential for multicentricity must also be borne in mind.

Theoretically, the non-aggressive behaviour of the renal oncocytoma justifies a less radical surgical approach to treatment. There are however a number of practical points which indicate that in the majority of cases a standard radical nephrectomy remains the treatment of choice. The most serious consideration is the capacity of a small minority of oncocytomas to infiltrate the perinephric fat, metastasize to local lymph nodes and even metastasize widely. Another serious problem is the difficulty in pre-operative diagnosis already discussed. Furthermore, renal oncocytomas are frequently of a large size at time of diagnosis (Table 1) and the consequent destruction of the renal parenchyma may render the kidney beyond salvage. It should be noted that huge size is not indicative of inoperability and a good result can be expected from radical nephrectomy, even in tumours in excess of 15 cm in diameter.

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