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Renin-producing renal cell carcinomas – clinical and experimental investigations on a special form of renal hypertension

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Summary. The pathogenetic relationship between tumour and hypertension was investigated in 129 patients with renal cell carcinoma, of whom 41 (31.8%) were hypertensive. Of these 41 patients with renal tumours and hypertension, 6 (14.6%) were found to have primary reninism. In these patients the plasma renin activity in blood from the renal veins showed a tumour kidney to contralateral kidney ratio of between 4 and 7, and 2 patients also had secondary hyperaldosteronism. In the same 6 cases the renin content in the renal tumour tissue was significantly higher than that in tissue from the adjacent tumour-free renal cortex of the ipsilateral kidney. Immunohistochemical demonstration of renin in the tumour was only possible in these 6 cases. In 5 of these patients blood pressure returned to normal following nephrectomy; in the 6th case there was a drop in blood pressure after nephrectomy. In 3 renin-positive tumours examined, autonomous renin production was demonstrated in cell culture. Renin-producing renal cell carcinomas are an uncommon cause of renal hypertension. The differential diagnosis of hypertension should therefore also include renal tumour.

Key words: Renal cell carcinoma – Renin – Endothelial cells – Hypertension

Hypertension as a consequence of unilateral or bilateral renovascular or renoparenchymal disease occurs in 5–7% of the total hypertensive population [1, 5]. Renal hypertension is thus the most common cause of secondary hypertension.

A rare cause of renal hypertension is a renal tumour with autonomic renin production. This form of renal hypertension is thus the consequence of "primary reninism" [3]. Three different types of renin producing tumour are known: tumours of the juxtaglomerular cells [19, 20, 22], nephroblastomas [4, 17, 24, 25, 34] and renal cell carcinomas [7, 8, 11, 14–16].

Patients ($n = 129$) with renal cell carcinomas from our own patient population were studied with respect to a possible causal pathogenetic relationship between tumour and hypertension. For this purpose the plasma renin activity (PRA) was determined in the peripheral venous blood and selectively in renal vein blood and the renin content measured in homogenates of tumour tissue and of tumour-free ipsilateral renal cortex. In order to detect secondary hyperaldosteronism, aldosterone was determined in peripheral venous blood. Immunohistochemical methods were used to identify the source of renin production within the tumour. An attempt was also made to demonstrate autonomous renin production in cell culture.

Materials and methods

In a group of 129 consecutive patients presenting with renal cell carcinoma there were 41 (31.8%) with hypertension. In all 129 patients the PRA was determined in peripheral venous blood and selectively in renal venous blood using a commercial renin radioimmunoassay (RIA; Baxter Travenol Diagnostics, Cambridge, Mass., USA). In 14 patients with hypertension the selective collection of renal vein blood was performed 30 min after a single oral dose of 25 mg captopril. In 54 patients a conventional aldosterone RIA (Abbott Diagnostics, Wiesbaden, FRG) was used to measure the *aldosterone* concentration in the peripheral venous blood in addition to determination of the PRA.

For calculation of the *tissue renin content* 1 g tumour tissue and 1 g adjacent tumour-free renal cortex were excised from the removed tumour kidney, placed in a test tube, treated with phosphate buffer (pH 7.4) and homogenized (2 min at 10,000 rpm Power Control Unit; Kinematic, Littau-Lucerne, Switzerland). The homogenates were centrifuged for 10 min at 4,000 rpm. The renin contents of the two tissue samples were determined in the supernatant using a commercial renin-RIA (Pasteur, Paris, France). This RIA, which uses two monoclonal antibodies of high specificity and affinity, permits direct and quantitative determination of the active form of the renin enzyme.

The *protein contents* in the homogenates of tumour and renals cortex were determined by the biuret method and for each tissue specimen the renin content was expressed as a fraction of the protein content (μg renin/g protein).

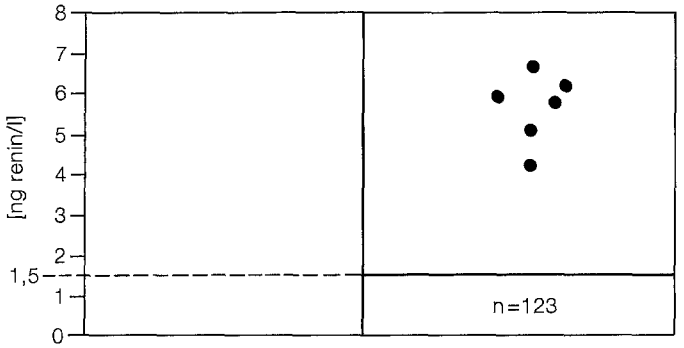


Fig. 1. Ratio of plasma renin activity (PRA) tumour kidney/contralateral kidney in 129 patients which renal cell carcinoma. Individual data points are only shown for those patients with a ratio >1.5

Table 1. Ratio of plasma renin activity (PRA) in selectively obtained renal vein blood before and after administration of captopril (*C*)

Tumour	Condition	PRA ratio
		tumour side/ contralateral side
4	Before C	6.1
	After C	7.3
5	Before C	6.1
	After C	8.2
6	Before C	6.5
	After C	7.6

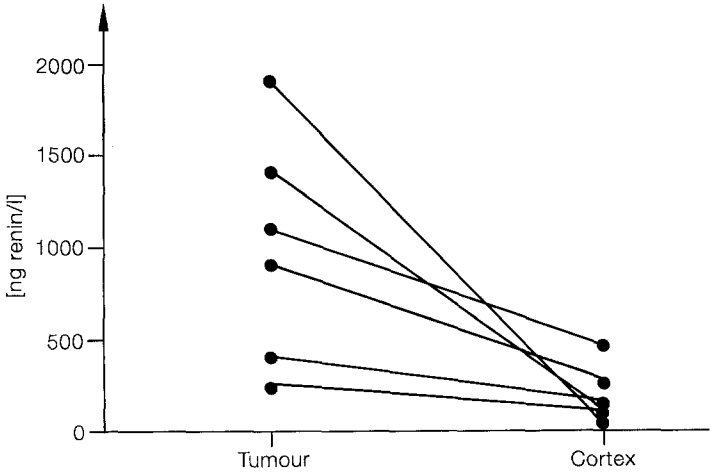


Fig. 2. Renin levels in tumour and ipsilateral tumour-free renal cortex in 6 patients with renal cell carcinoma

For the *immunohistochemical* examination 1-g portions of tumour tissue and adjacent cortex tissue were fixed in Bouin's fluid and processed by the peroxidase-antiperoxidase (PAP) method of Sternberger et al. [28]. We used a polyclonal renin antibody produced in our own laboratory which binds active and inactive renin. The dilution of the primary antiserum was 1:2,000. Renal cortex was incubated as positive control. Sections of renin-positive tumour tissue were stained with haematoxylin to identify tumour epithelial cells and counterstained with Schiff's reagent to evaluate the capillaries.

For determination of renin in *cell culture*, in each of 7 cases tumour tissue obtained under sterile conditions was cut into pieces measuring 2×2 mm, placed in a culture box at 37°C in an atmosphere of 5% CO^2 and 95% air and left to grow for 6 months. Each culture vessel contained 10 ml culture medium, which was changed every other day. Dulbecco's modified Eagle's medium (DMEM) (Gibco Biocult, Karlsruhe, FRG) was the basic culture medium used. We added 1 ml/100 ml penicillin-streptomycin (10,000 IU/ml), 1 ml/100 ml non-essential amino acids and 10% fetal calf serum to the commercially available synthetic medium. The renin activity in the culture medium was determined using the renin RIA (see above). If there was a measurable renin concentration the cultured cells were examined immunohistochemically using the renin antibody prepared in our own laboratory (see above).

Results

Clinical findings

In 5 out of 41 hypertensive patients with renal cell carcinoma, tumour nephrectomy led to normotension. In a 6th patient the blood pressure fell from 190/90 mm Hg to 165/90 mm Hg. These 6 patients (14.6%) no longer required antihypertensive treatment. In the remaining 35 patients the blood pressures were still raised after tumour nephrectomy and further antihypertensive medication was necessary.

PRA, captopril test, plasma aldosterone and tissue renin

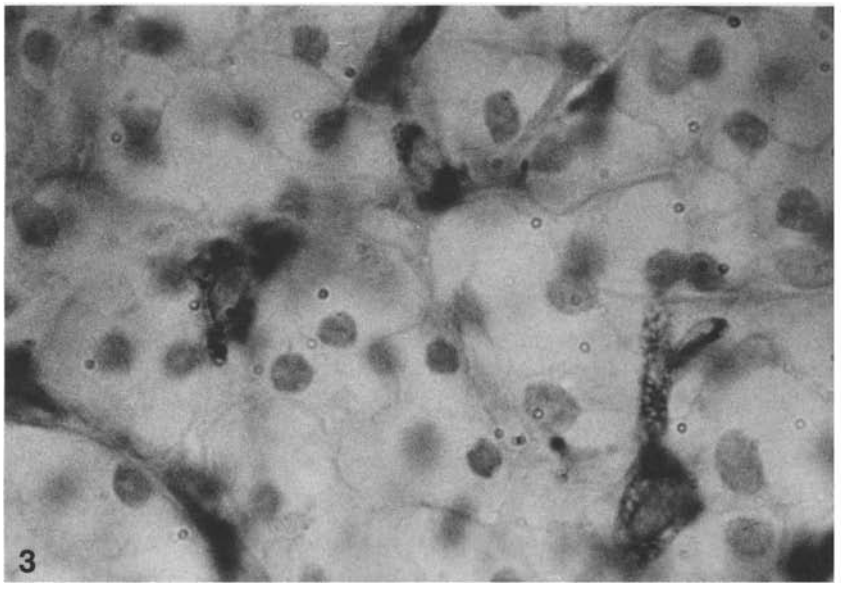
Peripheral PRA was within the normal range in all tumour patients. In 6 of 41 (14.6%) patients, selective determination of PRA in renal vein blood showed a difference between the two kidneys. The tumour kidney to contralateral kidney ratio for PRA in these patients was between 4 and 7, while in the remaining 123 cases the ratio was less than 1.5 (Fig. 1).

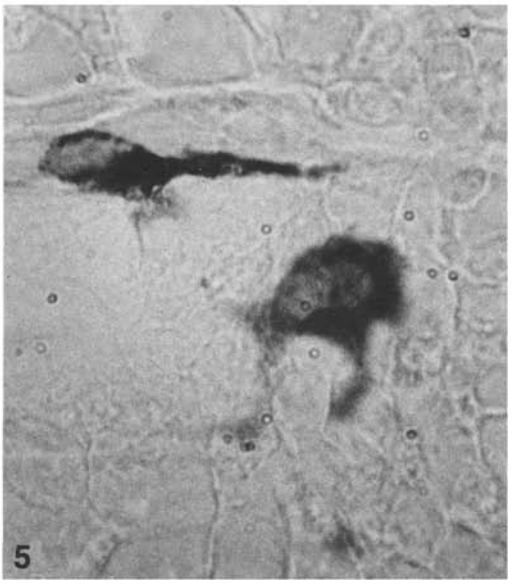
A ratio of greater than 1.5 was only found in the 6 patients whose blood pressure decreased or returned to normal after nephrectomy.

In 3 of the 6 patients with significantly different PRA levels in the two renal veins the administration of captopril accentuated the difference between the two sides and led to greater PRA ratios (Table 1).

Of the 57 patients in whom the peripheral aldosterone concentrations were measured, 2 had renal vein renin ratios of greater than 1.5. Only these 2 patients were found to have secondary hyperaldosteronism with hypernatraemia and hypokalaemia.

Significantly higher renin concentrations in the renal tumour tissue than in tissue from the adjacent tumour free cortex of the ipsilateral kidney were only found in the 6 patients with raised PRA in the blood from the renal vein of the tumour kidney (Fig. 2). The renin content per gram of protein in the tumour homogenate was on average 1.7 µg renin/g protein, while that in the renal cortex homogenate averaged 0.1 µg renin/g protein ($P<0.001$).





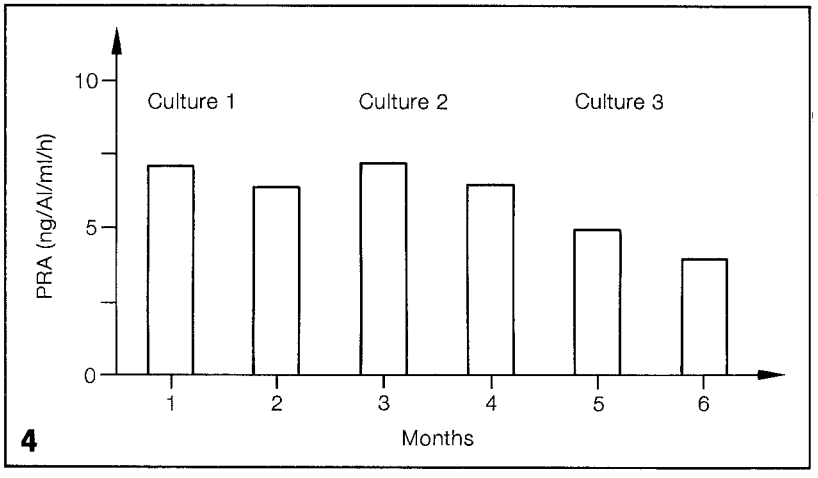


Fig. 3. Renin-positive vascular wall cells arranged in clusters. Tumour cells counterstained with haematoxylin. Original magnification ×100

Fig. 4. Detection of PRA in the incubation medium of the cell culture in three successive cell generations of the same tumour

Fig. 5. Immunohistochemical demonstration of renin-positive cells in a renal cell carcinoma grown in cell culture. Original magnification ×100

Angiographic findings

The tumour kidneys of the 6 hypertensive patients with elevated levels of renin activity in the plasma of the ipsilateral renal vein and raised renin concentrations in the tumour tissue presented no characteristic angiographic findings. The tumour diameters varied between 3 and 10 cm, 4 tumours being located centrally and 2 peripherally. All the tumours were hypervascular but there was no evidence of compression of renal arteries or of arteriovenous fistula.

Morphological findings

In the immunohistochemical assays renin was only demonstrated in the tumours of the 6 patients who also had elevated renin levels in the corresponding renal vein plasma and tumour tissue homogenates. The antigen was found in the walls of the tumour capillaries in cells which were irregularly distributed and sometimes arranged in clusters (Fig. 3). The cells often possessed cytoplasmic processes and were thus distinguishable from the epithelioid cells of the juxtaglomerular apparatus which were labelled in the adjacent tumour-free tissue of the renal cortex.

Demonstration of renin in cell culture

In 3 cases of hypertension and elevated renin concentrations in plasma and tissue we were able to demonstrate autonomous renin production by the tumour tissue grown in culture.

The explants, which were composed of variously compact tissue pieces, survived in culture for 6 months. During this period, renin activity was demonstrated continuously in the incubation medium in three successive cell generations of the same tumour tissue (Fig. 4). Immunohistochemical examination showed renin-positive cells which corresponded morphologically to the renin-positive vascular wall cells demonstrated immunohistochemically in tumour tissue (Fig. 5).

Discussion

Secondary or symptomatic hypertension, which accounts for 5–7% of all cases of hypertension [1, 5], is frequently of renal origin. As renal hypertension is often amenable to causal surgical treatment it is therapeutically important to distinguish diagnostically between this and other forms of hypertension. This applies particularly to all forms of renovascular disease, all unilateral alterations of the renal parenchyma and to urinary obstruction [18, 21, 23, 27, 33, 35].

The pathogenesis of renal hypertension is clear today on the whole. The central role is played by the renin-angiotensin system, which is involved in blood pressure regulation both indirectly through stimulation of aldosterone secretion, and thus via sodium-water homeostasis, and directly through action on the arterioles.

A rare cause of renal hypertension is a renin-producing renal tumour. The autonomous renin production by such tumours was described by Conn et al. [3] as primary reninism. Although most reports of renin-producing tumours only describe individual cases [7, 10–12, 15, 16, 26, 31, 32], their clinical significance by far exceeds their frequency.

In the prospectively studied patient population presented here, 41 (31.8%) of 129 patients with renal cell carcinomas were found to have arterial hypertension. In 6 patients we were able to show that there was a causal-pathogenetic relationship between the tumour and hypertension.

The fact that in these 6 patients blood pressure returned to normal after tumour nephrectomy suggested that there was a relationship between tumour and hypertension. The high ratio found on selective determination of renin in the renal veins was indicative of renin-induced hypertension. While in renal hypertension of other origin a ratio of greater than 1.5 is a sign of renal hypertension [18, 23, 24, 27, 35], the ratio in the 6 tumour patients was between 4 and 7. In 3 of the 6 cases the difference between the two sides was accentuated by administration of captopril.

As the peripheral PRA was within the normal range in all tumour patients, measurement of the active renin in the peripheral blood is not suitable either as a tumour marker in renal cell carcinoma or for elucidation of renal hypertension.

Secondary hyperaldosteronism as an indirect indication of primary hyperreninism was found in only 2 patients, who also had elevated renal vein renin ratios. It follows from this that activation of the renin-angiotensin-aldosterone system must play a central role in the pathogenesis of tumour-related renal hypertension.

There are basically three mechanisms which can be discussed as possible causes of enhanced activity of the renin-angiotensin-aldosterone system in renal tumours. Given the appropriate size and location the tumour can, like a solitary cyst [35], compress one or more segmental arteries leading to ischaemia of the corresponding region, which can be the cause of renovascular hypertension. An arteriovenous fistula within the tumour can likewise lead to ischaemia of the normal renal tissue. This mechanism also represents a special type of renovascular hypertension. The third causal mechanism was first pointed out by Linder in 1947 [14]. In 2 cases of renal cell carcinoma and hypertension he observed that blood pressure returned to normal after removal of the tumour kidney although, being situated in the pole of the kidney, these tumours could not have been the cause of renal ischaemia. The capacity of the tumour cells for autonomous renin production postulated by Linder [14] as the cause of renal hypertension has meanwhile been confirmed [36].

In our own population we were able to rule out compression of segmental arteries and arteriovenous fistula within the tumours on the basis of the angiographic examinations. The findings in cell culture prove that the renal cell carcinoma is capable of autonomous renin production.

The introduction of immunohistochemical techniques has made it possible to demonstrate renin morphologically in the cells using special antibodies [2, 6, 15–17, 26, 29, 30]. By using Schiff's reagent for examination of the capillaries we were able to assess the location of the renin-positive cells in our own tumour material. The morphology and location suggest that they are endothelial cells. It is known that these cells have the capacity for renin production. Lilly et al. [13] and Kifor and Dzau [9] were able to demonstrate renin expression by aortic endothelial cells in cell culture. In our own population the renin-positive vascular wall cells were found only in the 6 renal cell carcinomas with hypertension which were associated with elevated renin levels in plasma and tissue. None of the other tumours examined displayed any renin-positive cells. Lindop and Fleming [15], on the other hand, found perivascular, granulated, renin-positive cells in the renal tumours in 8 of 17 normotensive cases. It is of note that the tumour renin was present mainly in an inactive form, i.e. a precursor of active renin, which was measured biochemically in the plasma. The antibody used by these authors possesses different properties from that used in our investigations as the former demonstrates tissue renin and at the same time cross-reacts with the inactive plasma renin. As the polyclonal antibody used in the present study binds both active and inactive renin we can draw no conclusions as to the biological activity of the renin demonstrated immunohistochemically in the renal cell carcinomas. However, this is not possible with other antisera used to date either.

We do not yet know the role played by the renin-angiotensin system in renal tumours. The close relationship between renin-positive cells and blood vessels in the renal cell carcinoma suggests that angiotensin II might represent a growth factor for blood vessels which increases the vascularization of the tumour.

The results of our investigations show that 14.6% of renal cell carcinomas can, as paraneoplastic syndrome, cause hypertension through increased secretion of active renin produced in the vascular wall cells. This increased renin secretion, which can be augmented by captopril, can only be detected by selective collection of blood from the renal veins and not by determination of the PRA in peripheral blood. Determination of renin in tumour homogenate and extracts from ipsilateral, tumour-free renal cortex and cell culture investigations shows that increased levels of renin found in the tumour are responsible for the renal hypertension.

The differential diagnostic considerations for raised blood pressure should therefore include a renal tumour as the cause of the hypertension and ultrasonography of the kidneys should be performed at every check-up examination. While the most common type of tumour in elderly patients is a renal cell carcinoma and in children a Wilms' tumour, in young patients the possibility of a small benign tumour of the juxtaglomerular apparatus [19, 20, 22] must also be considered. Such tumours can be located by selective determination of PRA and selective angiography. In the case of small tumours the hypertension can be treated causally by organ-sparing tumour resection. In cases of larger neoplasms tumour nephrectomy at the same time serves to treat the hypertension.

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