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Abstract

An unusual case of orbital tumor with high renin content and severe hypertension is described. The patient was a 15-year-old girl with juvenile hypertension (200-140 mmHg) associated with right exophthalmos and hypokalemia. The patient showed extremely high levels of plasma renin activity and plasma aldosterone concentration. No difference was present in plasma renin activity from either side of the renal veins. Preoperatively, hypertension responded to treatment with spironolactone. The tumor could not be completely removed because of intracranial metastasis and infiltration, and the hyperreninemia and secondary hyperaldosteronism persisted. The renin content in the orbital tissue was 1,403-2,225 ng/angiotensin I generated/h/g wet weight of tissue. The postmortem histopathologic diagnosis was orbital hemangiopericytoma. This is the first case of extrarenal (ectopic) renin-secreting (or -producing) hemangiopericytoma of the orbital origin. Furthermore this case is worthy of note in the point of view of the presence of the extrarenal renin-angiotensin system, particularly in the brain.

KEYWORDS: renin producing tumor, hemangiopericytoma, juvenile hypertension, hypokalemia, orbital tumor

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—— BRIEF NOTE ——

A CASE OF ECTOPIC RENIN-SECRETING ORBITAL HEMANGIOPERICYTOMA ASSOCIATED WITH JUVENILE HYPERTENSION AND HYPOKALEMIA

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Abstract. An unusual case of orbital tumor with high renin content and severe hypertension is described. The patient was a 15-year-old girl with juvenile hypertension (200-140 mmHg) associated with right exophthalmos and hypokalemia. The patient showed extremely high levels of plasma renin activity and plasma aldosterone concentration. No difference was present in plasma renin activity from either side of the renal veins. Preoperatively, hypertension responded to treatment with spironolactone. The tumor could not be completely removed because of intracranial metastasis and infiltration, and the hyperreninemia and secondary hyperaldosteronism persisted. The renin content in the orbital tissue was 1,403-2,225 ng/angiotensin I generated/h/g wet weight of tissue. The postmortem histopathologic diagnosis was orbital hemangiopericytoma. This is the first case of extrarenal (ectopic) renin-secreting (or -producing) hemangiopericytoma of the orbital origin. Furthermore this case is worthy of note in the point of view of the presence of the extrarenal renin-angiotensin system, particularly in the brain.

Key words: renin producing tumor, hemangiopericytoma, juvenile hypertension, hypokalemia, orbital tumor.

The first case of renin-secreting renal tumor or juxtaglomerular cell tumor was described by Robertson *et al.* (1) and Kihara *et al.* (2) This very characteristic hypertentive condition associated with hyperreninemia and secondary aldosteronism is now considered surgically remediable. In Japan four cases have been reported (2-5). In this paper we report an unusual case of extrarenal renin-secreting hemangiopericytoma of orbital origin associated with brain and lung metastases.

Case report. On April 9, 1974, a 15-year-old girl was admitted to our hospital with right exophthalmos that had developed gradually over a period of

11 years and produced systemic hypertension and hypokalemia. High blood pressure (200–140 mmHg) was noted for the first time 3 months before admission. She also complained of nasal obstruction and right visual disturbance due to the right orbital tumor.

The laboratory report indicated iron-deficiency anemia, but blood urea nitrogen and creatinine levels were within the normal range throughout the clinical course. Liver function data were within the normal range. Cerebral angiography showed a large angioma-like shadow inside the right expanded orbit. The hypertensive ocular fundus was not remarkable. Plasma renin activity (PRA) showed sustained high levels, and hyperaldosteronemia and hypokalemia (3.0–3.9 mEq/l) were simultaneously present. Urinary catecholamines were normal or high normal, and the phentolamine test showed a negative response. Slight glucose intolerance was noted. The Robertson-Kihara syndrome was suspected. The results of the dripped intravenous pyelography and kidney scintigrams were not remarkable, but the existence of an arterio-venous fistula at the main branch of the left renal artery was suspected on the retrograde aortography examination. However, no differences were evident in PRA levels between blood from either side of the renal veins (Table 1). After administration of spironolactone, high blood pressure was also corrected.

TABLE 1. PLASMA RENIN ACTIVITY (PRA) AND PLASMA ALDOSTERONE CONCENTRATION (PAC) OF THE ECTOPIC RENIN-SECRETING ORBITAL TUMOR PATIENT

Blood sampling site	PRA (ng/ml/h)	PAC (ng/100 ml)
Left renal vein	13.80	13.48
Inferior vena cave		
Below renal veins	17.16	15.05
Above renal veins	15.44	16.17
Abdominal aorta		
Above renal arteries	15.36	24.51
Peripheral Vein	14.36	17.64

On June 6, 1974, an orbitotomy was undertaken. The tumor was 65×70×50 mm, well-capsulated, circumscribed, hard, pulsating, haemorrhagic and 140 g in weight (Fig. 1). Complete excision was not possible because of metastasis and infiltration to the intracranial region (mainly frontal lobe) and adjacent parasinutic spaces.

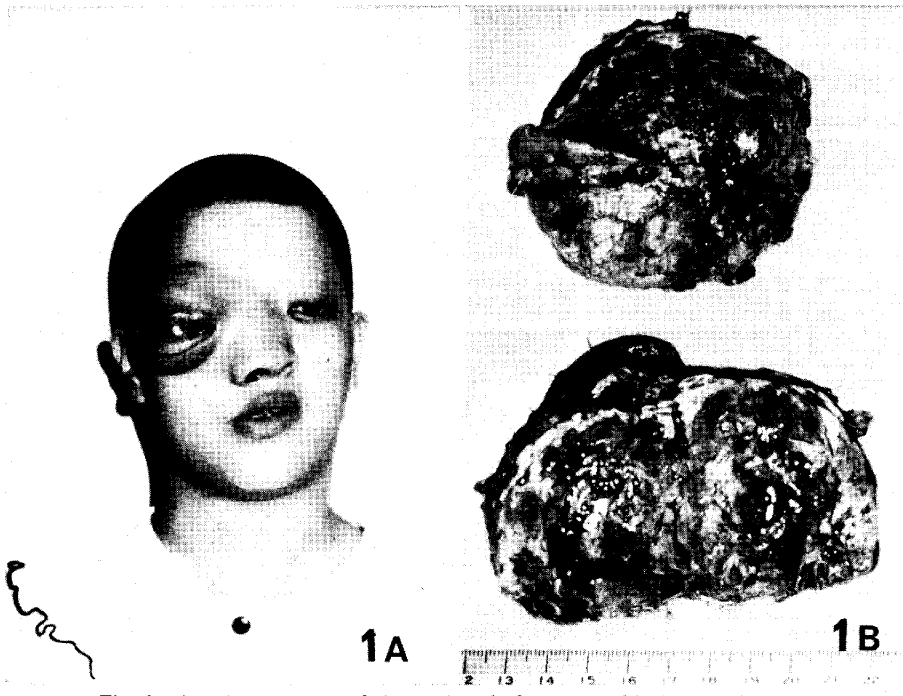

Fig. 1. A.: Appearance of the patient before the orbital operation.
B.: Gross appearance of the tumor excised at the orbital tumor.

Postoperatively, the blood pressure was lower for about half a year, but hyperreninemia and secondary hyperaldosteronism persisted. Thereafter, hypertension again became apparent. The tumor infiltration into the intracranial region could not be controlled. At 9 months after surgery, the patient developed diabetes insipidus-like polyuria (7,000–9,800 ml/day) and in the final stages, respiratory insufficiency. She died on July 31, 1975, and an autopsy was performed 5 h after death. The main findings were: orbital hemangiopericytoma associated with metastasis to the intracranial region, mainly the right frontal lobe and both lungs; marked bronchopneumonia; slight but diffusse hyperplasia of the juxtaglomerular cells in both kidneys; slight hyperplasia of the zone glomerulosa of the adrenal gland with much lipid content.

Renin-angiotensin-aldosterone axis. Extremely high PRA levels (10.8–28.2 or more ng/ml/h; normal range, 0.5–4.0 ng/ml/h) and high plasma aldosterone concentration (PAC) (10.1–135.1 ng/dl; normal range, 3–17 ng/dl) were evident during hospitalization. There was almost no PRA response to salt restriction and upright posture (Table 2, Fig. 2).

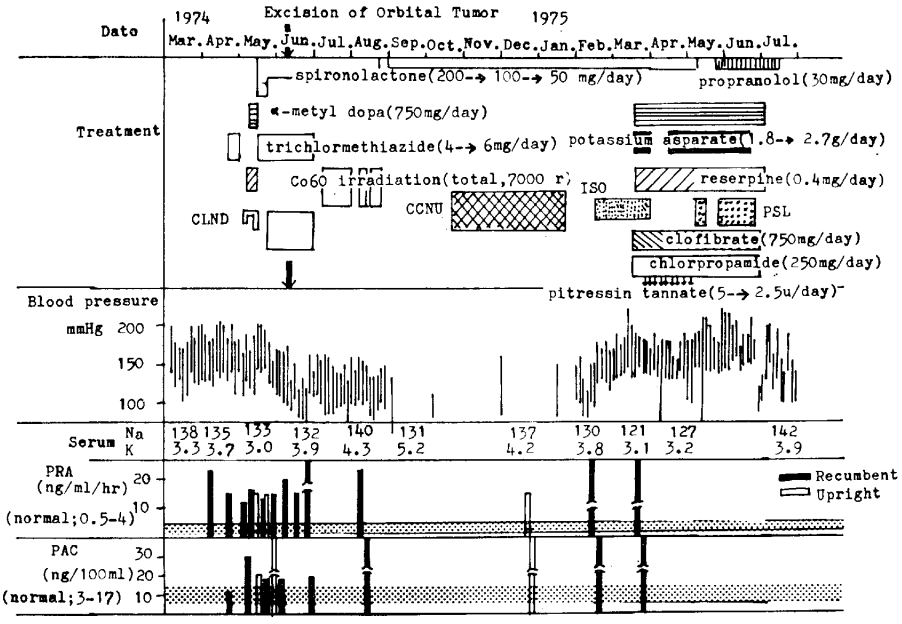

Fig. 2. Clinical coursc before and after operation in the patient with ectopic renin-secrcting orbital tumor. CLND; clonidin hydrochloride (0.15, 0.075, 0.225, 0.45 mg/day) CCNU; 1-(2-chloroetyl)-3-cyclohexyl nitrosourea (total, 360 mg), ISO; isosorbitol (90 ml/day) PSL; prednisolone (20, 30, 50 mg/day), PAC; Plasma aldosterone concentration, PRA; plasma renin activity.

TABLE 2. DATA RELATED TO THE RENIN-ANGIOTENSIN-ALDOSTERONE AXIS IN THE ECTOPIC RENIN-SECRETING ORBITAL TUMOR PATIENT

Condition	Date	Diet	Supine position (Upright posture) PRA (ng/ml/h)	PAC (ng/100ml)	Blood pressure (mmHg)	Serum Na (mEq/l)	Serum K (mEq/l)	Anti-hypertensive drugs
Preoperative	4/24/74	(L 3-5)	13.46	10.10	208/140	135	3.7	—
	5/ 8/74	L (3-5)	10.76	28.13	210/140	133	3.7	C
	5/15/74	N	17.26 (15.50)	— (20.38)	182/140	133	3.0	M, R
	5/18/74	L (6)	12.94 (14.80)	18.40 (55.44)	192/130 192/130	137 137	3.6	S
At operation	6/ 6/74	—	19.86[a]	—	160/90	135	3.3	—
Postoperative	6/28/74	N	29.40	19.09	158/120	135	4.3	C, T
	8/10/74	N	22.62	36.05	140/80	133	4.6	S
	12/25/74	N	(13.42)	(37.70)	160/80	137	4.2	S
	2/20/75	N	28.20	135.05	170/146	130	3.8	S
	3/26/75[b]	N	35.22	93.06	200/120	130	3.5	M, R, S

a From blood around the oribital tumor, *b* Diabetes insipidus-like polyuria present.
PRA, Plasma renin activity. PAC, Plasma aldosterone concentration. ( ): Vaiue obtained after maintaining an upright posture. L: Low sodium intake (gram/day). N: Normal sodium intake (12-15 gram/day). C: Clonidine. M: alpha-methyl dopa. R: reserpine. S: Spironolactone. T: Trichlormethiazide.

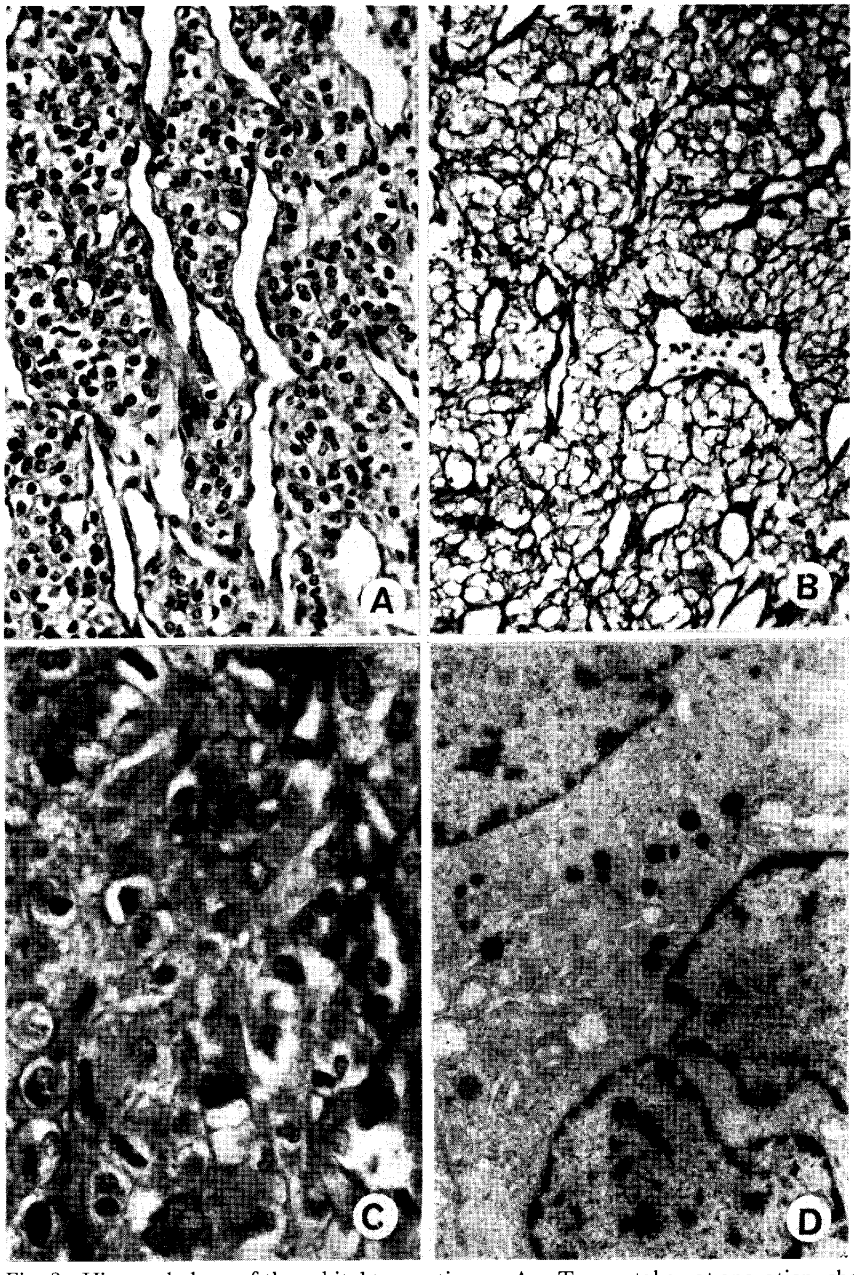

Fig. 3. Histopathology of the orbital tumor tissue. A.: Tumor taken at operation, showing sheets of polygonal cells with epithelioid appearance between endothelial-lined vascular spaces. H-E ×200. B.: Reticulin fibers surrounding tumor cells and separating them from the endothelial lining. Silver impregnation, Watanabe's method. ×200. C.: Tumor cells with some intracytoplasmic granules. Bowie stain. ×1000. D.: Tumor cells showing rough endoplasmic reticulum, mitochondria and some granules of varing size. ×9000.

Histopathology of tumor tissue. Postmortem histopathologic examination of the tumor confirmed the earlier histologic findings of specimens obtained during surgery. The hemangiopericytoma was verified by reticulin silver staining. Many mast cells and some fine granules positive to Bowie's stain were observed. Electron microscopic observations of tumor cells indicated the presence of mostly round granules, but rhomboid granules were not found (Fig. 3).

Renin content of tumor tissue. The renin content of the orbital tumor was measured in three separate samples by radioimmunoassay. The values were 1,403, 1,429, and 2,225 ng angiotensin I generated/gram wet weight of tissue. This renin content is 4.3–6.7 times higher than the renin content of adjacent renal cortex of the juxtaglomerular cell tumor reported by Terashima *et al.* (4) These values were determined by the same radioimmunoassay method and were measured by the same investigators in the same institute (Table 3).

TABLE 3. TISSUE RENIN CONTENT IN RENIN-SECRETING TUMOR PATIENTS

Investigator	Renin Content[a] (ng/AT I generated/h/g wet weight of tissue)	
	Tumor	Renal Cortex
Terashima *et al*[a] (4)	1.6×10^6	3.3×10^2
Present Case[a]	$1.4\text{–}2.2\times10^3$	Not done

a The values were determined by the radioimmunoassay method described by Conn *et al.* (6) and were measured by Prof. S. Fukuchi and Dr. T. Miura.
AT I: Angiotensin I

Discussion. Primary reninism proposed by Conn *et al.* (6) includes the Robertson-Kihara syndrome (1, 2), renin-secreting Wilms tumor (7), renin-secreting clear cell carcinoma of the kidney (8) and ectopic renin-secreting tumor. There are five case reports (9–12) on extrarenal renin-secreting tumor including our case (Table 4). Henderson (13) reported 16 cases of orbital hemangiopericytoma, but no case was associated with hypertension.

In our case the following points are noteworthy: (a) This patient progressed to a malignant clinical course and death whereas the postoperative clinical prognosis in the Robertson-Kihara syndrome is usually good after nephrectomy. (b) This case disclosed a pathophysiologic state of dominant high PRA rather than hyperaldosteronism and may illustrate the existence of other neoplasms of extrarenal origin in Conn's proposed primary reninism. (c) Treatment with spironolactone alleviated hypokalemia and high blood pressure. (d) Juxtaglomerular cells on both sides of the kidneys showed hyperplasia possibly because of the long-term administration of spironolactone. (e) Conn (6) emphasizes that the high level of PRA which does not respond to large variations of

sodium intake, but does respond to assumption of the upright posture will become an important adjunctive diagnostic criterion for primary reninism. The

TABLE 4. EXTRARENAL RENIN-SECRETING TUMORS REPORTED BY VARIOUS INVESTIGATORS

Investigator	Patient Age	Sex	Hyper-tension	Renin Content of Tissue (gm/tissue)	Origin	Histopathology
Hauger-Klevene (9)	38	M	Absent	28 ng AT II	Mediastium and lung	Oat cell carcinoma
Jacob et al. (10)	52	F	Present	Not done	Pancreas	Non-insulin secreting cancer
Cox et al. (11)	14	F	Present	Not done	Liver	Harmatoma
Genest et al. (12)	37	F	Present	4.4×10^{4}ng AT I	Lung	Undifferentiated lung carcinoma
Yokoyama et al. (Present case)	15	F	Present	$1.4\text{-}2.2\times10^{3}$ng AT I	Orbit	Hemangiopericytoma

AT I: Angiotensin I, AT II: Angiotensin II

same result was found in our case. Furthermore, PAC increased with assumption of the upright posture and walking under sodium restriction. (f) This case is suggestive of an ectopic hormone-producing tumor in the light of the recently reported existence of an extarenal iso-renin angiotensin system, particularly in the brain (14). (g) The extrarenal and ectopic renin-secreting tumor is unusual, this being the first case of a brain tumor producing high levels of renin-like substance and causing systemic hypertension.

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