Renin-producing serous cystoadenocarcinoma of the ovary: a case report

H. Iwamoto[1], S. Hirata[1], T. Honda[1], H. Fukasawa[1], N. Kimura[2], K. Hoshi[1]

[1]Department of Obstetrics and Gynecology, Yamanashi Medical University, Yamanashi,
[2]Department of Pathology and Laboratory Medicine, Tohoku Rosai Hospital, Miyagi (Japan)

Summary

Background: Only a few renin-producing ovarian tumors have been reported, and most such ovarian tumors have been sex cord/stromal tumors. Renin-producing ovarian epithelial tumors are quite rare.

Case: A 46-year-old woman presented with hypertension and hypokalemia. Examinations of the patient revealed elevated plasma renin activity, hyperaldosteronism and a pelvic mass. Subsequently, a right ovarian tumor mass was resected. Microscopic observation of the tumor revealed a well-differentiated serous cystadenocarcinoma. Immediately after surgery, blood pressure, serum potassium, plasma renin activity and plasma aldosterone levels returned to normal ranges. RT-PCR analysis and immunohistochemical staining of this tumor indicated that it was producing renin.

Conclusion: This is the first report of a renin-producing ovarian serous cystadenocarcinoma.

Key Words: Renin-producing ovarian tumor; Hyperreninism.

Introduction

Patients with renin-producing tumors are characterized by high circulating active renin and aldosterone levels, accompanied by hypertension and hypokalemia. Although such tumors are an unusual cause of secondary hypertension, they must be considered in the differential diagnosis of hypertension associated with hypokalemia. Most reported cases are renal tumors that are thought to arise from the juxtaglomerular apparatus. Extrarenal renin-producing tumors are even more unusual.

This report describes a 46-year-old woman with hypertension and hypokalemia, in whom investigations revealed a renin-producing well-differentiated serous cystadenocarcinoma of the right ovary. Renin-producing ovarian epithelial tumors are quite rare. This is the first report of a renin-producing ovarian serous cystadenocarcinoma.

Case report

The patient, a 46-year-old gravida two para two woman, consulted our hospital for headaches, hypertension and a pelvic mass. The patient had otherwise always been in excellent health. Her blood pressure was 170/110 mmHg on antihypertensive therapy (Nifedipine).

Laboratory investigation revealed normal renal function with a creatinine clearance rate of 78 ml/min (normal, 70-130 ml/min). Serum potassium was decreased to 2.8 mEq/l (normal, 3.4-4.8 mEq/l). Serum ALP and LDH were increased to 943 IU/l (normal, 92-231 IU/l) and 493 IU/l (normal, 118-213 IU/l), respectively. The tumor markers CA-125, CA 19-9, CA 72-4 and NSE were markedly elevated (Table 1). Plasma renin activity was elevated to 35.3 ng/ml/hr (normal, 0.2-2.7 ng/ml/hr) and plasma aldosterone was also elevated to 27.6 ng/dl (normal, 2.0-13.0 ng/dl).

Abdominal ultrasound and MRI scan confirmed a 13 x 11 x 9.5-cm pelvic mass consisting of an admixture of solid and cystic parts. Abdominal CT scan revealed no tumor in either kidney. Results of renography and renal angiography were normal, with no evidence of renovascular hypertension.

The patient underwent a laparotomy, at which a 542 g and 13 x 10.5 x 6.5-cm right ovarian tumor mass (Figure 1) was resected with the uterus, left ovary, omentum and retroperitoneal lymph nodes. Microscopic observation of the right ovarian tumor revealed a well-differentiated serous cystadenocarcinoma (Figure 1) with a ruptured capsule and malignant cells in the ascites (FIGO stage Ic). Immediately after surgery, blood pressure (100/60 mmHg), serum potassium, ALP, LDH, plasma renin activity and plasma aldosterone levels returned to normal ranges and remained stable (Table 1). After surgery, the patient was treated with two courses of intraperitoneal cisplatin and five courses of intravenous cisplatin, cyclophosphamide and doxorubicin.

To estimate the renin-producing capacity of this ovarian carcinoma, RT-PCR analysis was performed for the detection of renin mRNA. Total RNA was extracted from this carcinoma tissue according to the procedure of Chirgwin *et al.* [1]. Total RNAs of the normal portions of ovarian tissues were also extracted from subjects who underwent surgery for benign ovarian cysts. All patients were ethnically Japanese and gave

Table 1. — *Preoperative and postoperative serum potassium, tumor markers, plasma renin activity (PRA), and plasma aldosterone.*

	Normal Value	Preoperative	Postoperative (3 weeks)
K	(3.4-4.8 mEq/l)	2.8	4.5
ALP	(92-231 IU/l)	943	167
LDH	(118-213 IU/l)	493	142
CA 125	(-35.00 U/ml)	10,000.00	80.00
CA 19-9	(-37.00 U/ml)	750.00	20.25
CA 72-4	(-4.00 U/ml)	28.13	0.14
NSE	(-7.0 ng/ml)	12.6	4.35
PRA	(0.2-2.7 ng/ml/hr)	35.3	0.2
Aldosterone	(2.0-13.0 ng/dl)	27.6	10.0

Revised manuscript accepted for publication December 20, 2001

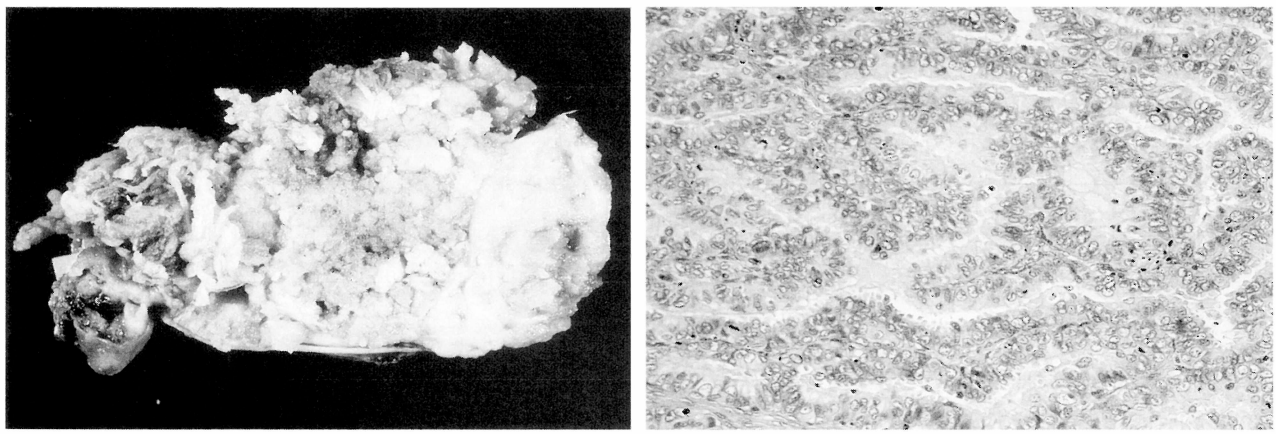


Figure 1. — Gross and microscopic appearance of the tumor. (A) Gross picture of the ovarian tumor. (B) Micrograph of the ovarian tumor tissue stained with hematoxylin and eosin.

informed consent. The sequences of the primers hRn5 (forward, 5'-CTG CAG ATG TTT GGA GAG GTC AC-3') and hRn6 (reverse, 5'-TCT AGA CAC CAG TCT TGA TGA GG-3') were derived from the human renin cDNA sequence [2]. In order to facilitate subcloning, additions of a few nucleotides were introduced. Since these primers were believed to flank the region including an intron on genomic DNA, the expected length of the RT-PCR products could be generated only from mRNA, and not from genomic DNA. Total RNAs from the samples were reverse transcribed to synthesize single-stranded cDNAs, and PCR was performed for 32 cycles at 94°C for 1 min, 55°C for 1 min and 72°C for 1 min. The RT-PCR product was confirmed to be a part of the human renin cDNA by nucleotide sequencing. As shown in Figure 2, renin mRNA was strongly detected in the carcinoma tissue, despite its weak expression in the normal ovarian tissues.

Using immunohistochemical staining, we carried out further studies of renin secretion by this carcinoma tissue. Staining was performed as described in a previous report [3]; in brief, after inhibition of endogenous peroxidase activity with 0.3% hydrogen peroxide in methanol, deparaffinized sections were incubated overnight at 4°C with rabbit anti-human renin antibody at a dilution of 1:1,500. The anti-human renin antibody was kindly provided by Dr. H. Miyazaki (Tsukuba Univ., Japan). This antibody recognizes active and inactive renin [4]. Antibody binding was demonstrated by a peroxidase-antiperoxidase technique. Peroxidase was detected by incubation in 3,3'-diaminobenzidine tetrahydrochloride and hydrogen peroxide for three minutes. As shown in Figure 3, immunoreactive renin was strongly present in the carcinoma tissue.

Discussion

In 1967, the first case of a renin-producing tumor was reported by Robertson *et al.* [5]. Since then, several cases of renin-producing tumors have been described. Most such tumors are of renal origin. Juxtaglomerular cell origin tumor [5-7] is the most common of these renal tumors, although rare cases of renal clear cell carcinoma [8-10], Wilms's tumor [10, 11], and mesoblastic nephroma [12] have also been reported. Only a few extrarenal renin-producing tumors have been reported in cases of pulmonary cancer [13, 14], pancreatic cancer [15], epithelial liver hamartoma [16], orbital hemangiopericytoma [17], paraovarian cancer [18], and fallopian tube adenocarcinoma [19]. Some cases of ovarian renin-producing tumors have also been described [20-23] and most such ovarian tumors have been sex cord/stromal tumors. Renin-producing ovarian epithelial tumors are quite rare.

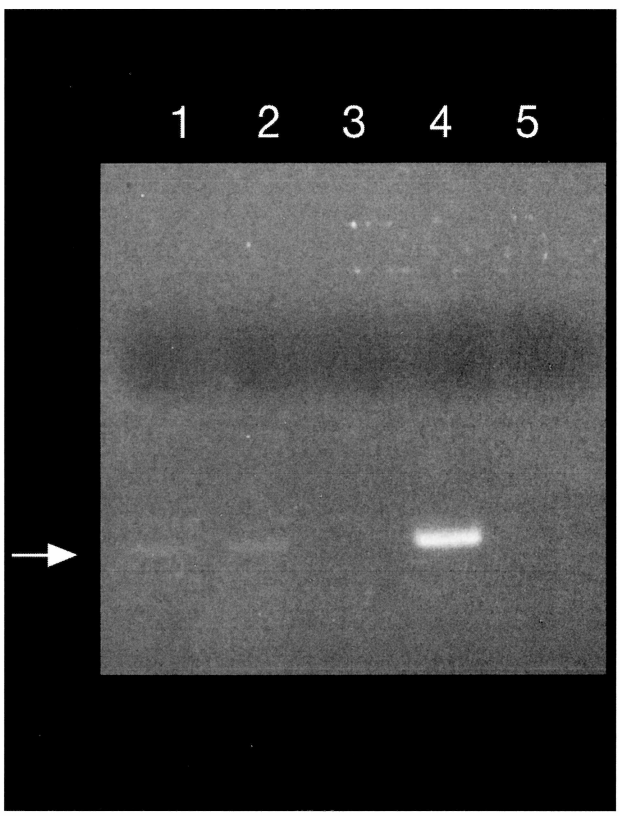
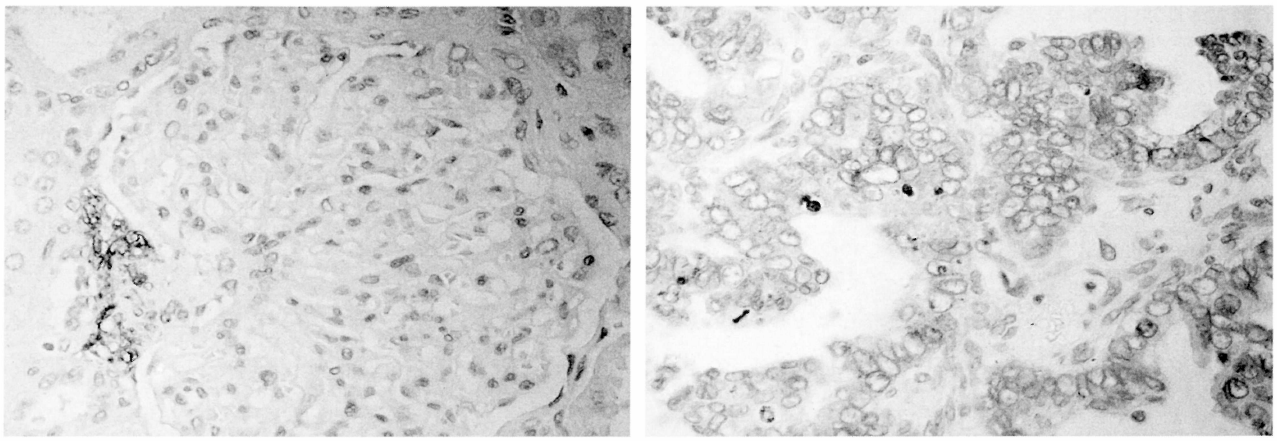


Figure 2. — RT-PCR products obtained with the primers hRn5/hRn6 from normal human ovaries and the renin-producing ovarian cancer. The RT-PCR products were electrophoresed on an agarose gel and stained with ethidium bromide. In order to examine whether contamination of reagents occurred in the present experiments, distilled water was simultaneously subjected to RT-PCR (RT-PCR-blank) and PCR (PCR blank). Lane 1: normal ovary (1), Lane 2: normal ovary (2), Lane 3: RT-PCR blank, Lane 4: ovarian cancer (this case), Lane 5: PCR blank.



A B

Figure 3. — Immunohistochemical staining of renin. Immunohistochemical staining was performed using anti-human renin antibody. (A) Immunostaining of a section of a kidney. Renin-containing cells in juxtaglomerular apparatus of atubular glomeruli were stained. (B) Immunostaining of the ovarian tumor tissue.

Only one case of a poorly differentiated ovarian carcinoma of epithelial origin has been reported [24].

In the present case, a clinical relationship between hypertension and ovarian tumor was demonstrated. High plasma levels of renin and aldosterone, with return to normal values after removal of the tumor, demonstrated that the tumor was producing renin. Further evidence that the tumor produced renin was obtained by RT-PCR analysis and immunohistochemical staining. The strong expression of renin mRNA and the staining of the tumor with renin antibodies indicated that the tumor was producing renin.

Recently, the ovary was found to produce prorenin and renin. The renin-angiotensin system in the ovary appears to play an important role in processes such as ovulation, steroid synthesis, folliculogenesis, oocyte maturation, and formation of the corpus luteum [25]. Although it was quite rare for the ovarian renin-angiotensin system to cause general hyperreninism, the histogenesis of these renin-producing ovarian tumors seems to be explained by the fact that the ovary produces renin.

In conclusion, we have for the first time reported a case of renin-producing ovarian serous cystadenocarcinoma. Reports of renin-producing extrarenal tumors emphasize the importance of considering extrarenal sources, including ovarian neoplasms, when investigating hyperreninism.

Acknowledgement

The authors gratefully acknowledge the cooperation of Dr. H. Miyazaki who kindly provided anti-human renin antibody for the study.

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Address reprint requests to:
K. HOSHI, M.D.
Department of Obstetrics and Gynecology,
Yamanashi Medical University,
Shimokato 1110, Tamaho, Nakakoma
Yamanashi, 409-3898 (Japan)