

# Multiple endocrine disorders manifested as gynecomastia in a patient with renal pelvis cancer

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## Abstract

A 95-year-old man was diagnosed with left pelvis cancer which presented with rapid tumor growth, multiple metastases, and bilateral tender gynecomastia. Elevated serum human chorionic gonadotropin(hCG), prolactin, estradiol, and progesterone were detected. The patient's condition rapidly deteriorated and he passed away.

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Abbreviations:

BPH– benign prostatic hyperplasia

UC – urothelial cancer

CT – computed tomography

MRI – magnetic resonance imaging

hCG – human chorionic gonadotropin

LH – luteinizing hormone

FSH – follicle-stimulating hormone

TSH – thyroid-stimulating hormone

T3 – triiodothyronine

T4 – thyroxine

## Abstract

A 95-year-old man was diagnosed with left pelvis cancer which presented with rapid tumor growth, multiple metastases, and bilateral tender gynecomastia. Elevated serum human chorionic gonadotropin(hCG), prolactin, estradiol, and progesterone were detected. The patient’s condition rapidly deteriorated and he passed away.

## Key Clinical Message

Poorly differentiated UC can secrete hCG and sex hormones, which can cause the autocrine progression of the tumor and paraneoplastic syndromes. Manifestation of paraneoplastic syndromes might be a hint for more aggressive management of UC.

## Introduction

Elevations of various tumor markers have been reported in urothelial cancer (UC) patients. We have previously reported a case of bladder UC that tested positive for four tumor markers including human chorionic gonadotropin (hCG)(9). Systemic effects resulting from the secretion of cytokines, growth factors, or hormones by tumor cells can cause paraneoplastic syndromes. The secreted molecules can work in a paracrine or autocrine mode (16). This can explain why paraneoplastic syndromes are usually present in high-grade aggressive tumors and are associated with a poor prognosis. The majority of the reports concerning UC describe paraneoplastic syndromes in bladder cancer. Renal pelvis cancer is rare and comprises approximately 5% of all urothelial carcinomas (15, 18).

Gynecomastia, enlargement of the male breast, is a common condition that can affect a man of any age. However, the highest prevalence occurs in older men, with as many as 65% having palpable gynecomastia(8). hCG is an analog of LH and can cause gynecomastia, if elevated. Ectopic production of hCG has reportedly been found in a variety of trophoblastic and nontrophoblastic neoplasms. It plays a role in cell transformation, angiogenesis, metastasis, and immune escape, key processes of carcinogenesis and tumor progression(21). We report an unusual case of renal pelvis cancer who presented with gynecomastia. Abnormalities of multiple hormones were also detected in this patient.

## Case presentation

A 95-year-old man has been treated for benign prostatic hyperplasia (BPH) with tamsulosin (an alpha-1 blocker) at our outpatient clinic. His symptoms were well controlled. His past history included chronic kidney disease (G4), hypertension, and hyperuricemia. During his regular visit in March 2020, he presented with microscopic hematuria. Pyuria was not seen and he had not had a history of macroscopic hematuria. computed tomography (CT) (Figure 1A) and magnetic resonance imaging (MRI) (Figure 1B) revealed a 3cm mass in the left renal pelvis. No hydronephrosis or metastasis was found. Urinary cytology was Class V, confirming the diagnosis of high-grade UC. The patient and his relatives refused surgical treatment and opted for follow-up. On regular CT (3 months and 1year later) the left pelvis tumor showed slow growth (Figure 1C, D). One year after the initial diagnosis no gynecomastia was detected (Figure 2A). The patient and the family still preferred regular follow-ups and the next CT was scheduled 6 months later. At the regular outpatient visit in September 2021, the patient presented with bilateral tender gynecomastia. On physical examination, there was an enlargement of both breasts which was painful to touch. There was no nipple discharge or overlying skin change. Testicular palpation did not reveal any testicular mass or testicular atrophy. On digital rectal examination, prostate was slightly enlarged without induration. A CT revealed bilateral gynecomastia (Figure 2B). No adrenal tumor was found. Left renal pelvis mass drastically increased in size and multiple bulky retroperitoneal lymph node metastases were present (Figure 1E, F). Liver metastases appeared (Figure 1F) and multiple bilateral lung metastases were detected by CT and chest X-P

(Figure 3B). A thorough lab workup for gynecomastia revealed elevated serum hCG of 142.4IU/mL (normal range 0-3), prolactin of 21.0 ng/mL (normal range 3.6-12.8 ng/mL), estradiol of 189.1pg/mL (normal range 19-51pg/mL), and progesterone of 39.8 ng/mL (normal range 0-06 ng/mL). Estradiol serum concentration in adult males is around 20 to 30 pg/ml (12). The serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were below detection levels ( $<0.1$ mlU/mL, normal range 0.8-5.7 mlU/mL and 2-8.3 mlU/mL, respectively). Serum total and free testosterone levels were significantly decreased to 46.3 ng/dL and 1.4 pg/mL, respectively (normal range 225-1039 ng/dL and 35–155 pg/mL, respectively). Serum hormone levels are summarized in Table 1. Thyroid-stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4) levels were normal.

Considering the poor prognosis, best supportive care was started with the family's consent. In October 2021, the patient was admitted to the hospital due to the deterioration of the general state of health. The patient passed away two weeks later at the age of 97 years.

## Discussion

Upper urinary tract UC is a relatively rare but often aggressive urologic malignancy(19). This patient presented with painful gynecomastia at the time of renal pelvis cancer progression. Gynecomastia can be caused by liver dysfunction, hyperthyroidism, and adrenal tumors. Gynecomastia is common among men with testicular failure, a state associated with elevated serum LH levels, and in patients with hCG-secreting testicular germ cell neoplasms (choriocarcinoma) (2). Also, multiple medications can play a role in the pathogenesis of gynecomastia, but none of such medications was prescribed to the patient. These most common causes of gynecomastia were ruled out in this patient. The presence of receptors for LH/hCG have been found in normal male breast tissue, benign gynecomastia tissue, and male breast carcinoma tissue(3). These findings explain how ectopic secretion of hCG may play a role in the pathogenesis of gynecomastia (8). Aberrant expression of hCG is a well-recognized phenomenon in various nontrophoblastic neoplasms including lung, gastric, renal carcinoma, and prostate(20).

Ectopic expression of hCG by UC has been recognized as being a relatively common observation(6). Expression of hCG by an established human bladder cancer cell line alongside with multiple cytokines (including G-CSF and G-CSF receptors) has been reported(22). Ectopic production of hCG by a highly malignant high-grade urinary bladder urothelial carcinoma is considered to be a well-established paraneoplastic syndrome. Elevation of serum hCG levels in patients with bladder carcinoma causing gynecomastia have also been reported(1, 14, 17). Most of these patients had high-grade malignancy and advanced disease. There are also published reports on primary choriocarcinomas of the renal pelvis (7, 13). Ectopic secretion of hCG by high grade upper urinary tract has been reported(20).

This patient had a very unusual presentation of a hyperestrogen state. Estradiol and hCG producing bladder UC can cause gynecomastia in men(1). Hormonal studies in this patient showed elevated hCG, prolactin, estradiol, and progesterone. Testosterone and gonadotropins were suppressed. Liver cirrhosis patients have a high prevalence of gynecomastia (about 40%). Those patients show significantly higher serum levels of estrogens and low serum testosterone levels. This patient had liver metastasis, however, liver function tests were normal. Moreover, there are no reports on gynecomastia in liver metastasis patients. Thus, liver dysfunction seems to be unlikely to cause gynecomastia in this patient.

Available data indicating that estrogen receptor signaling plays an important role in urothelial cancer(5). It has been demonstrated that patients with upper urinary tract (renal pelvis and ureter) UC positive for either estrogen receptor or progesterone receptor had a significantly higher risk of disease-specific mortality(11). Recent findings demonstrate that sex hormone receptor signaling plays an important role in the pathogenesis of urothelial cancer (reviewed in (10)). However, there is limiting information on aberrant steroidogenesis by UC. There is a possibility of conversion of androgens to estrogens by aromatase. However, testosterone was at a very low level in this patient (total and free testosterone levels were 46.3 ng/dL and 1.4 pg/mL, respectively), corresponding to testosterone castration level. There is a consensus that both total and free testosterone decline with age in males. However, serum testosterone is still several times higher than

castration level in men in their 80s and 90s(4, 12).

One can expect both high plasma estradiol and testosterone in a patient with increased hCG. However, testosterone was suppressed to castrate level in this patient. No testicular atrophy was detected on physical examination. The most plausible scenario is that estrogen produced by the tumor suppressed gonadotropin synthesis resulting in low serum testosterone in this patient. The source of high prolactin, estradiol, and progesterone can also be a tumor itself. The fact that the appearance of gynecomastia coincides with a rapid tumor progression might indicate that growing left renal pelvis urothelial carcinoma aberrantly produced sex hormones. As far as we know, there are no similar previous reports. The main drawback of this case report is that we were unable to obtain tumor tissue to confirm the expression of hCG and sex steroids in the tumor. However, no other source of ectopic hCG, prolactin, estradiol, and progesterone production was detected in this patient.

The limitation of the case is the absence of histopathological study of the renal pelvis tumor.

To our knowledge, this is the first report of aberrantly high levels of multiple hormones in an upper urinary tract cancer patient. Undifferentiated, highly aggressive UCs tend to express multiple cytokines and hormones, causing paraneoplastic syndromes. Ectopic hCG and steroid hormones production is thought to be an indicator of a higher grade of malignancy, poor histological differentiation, radioresistance, metastatic potential, and as a result, poor prognosis(23). This is in agreement with a theory of dedifferentiation and autocrine loop in highly malignant UC tumors.

### Conflict of Interest

The authors have no conflict of interest in the subject matter or materials discussed in this manuscript.

### Author contribution

SH and VB made substantial contributions to the conception, acquisition of data; VB conceived of the study, reviewed the literature, analyzed and interpreted the data, drafted and revised the manuscript. All authors read and approved the final version of the manuscript.

### Consent for publication

Written informed consent was obtained from the patients and their relatives for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor in Chief of this journal upon request.

### Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Figure legends

Figure 1. Axial CT scan (A) and axial T2W MRI (B) showed a mass 3cm in diameter in the left renal pelvis. The tumor was slow-growing, it slightly enlarged on the CT 3 months after the initial diagnosis (C). The tumor was slowly growing. CT scan axial image one year after the initial diagnosis (D). A bulky mass in the left retroperitoneum (E, F) and liver metastasis (encircled) (F) were detected 18 months after the initial diagnosis of the left pelvis tumor.

Figure 2. No gynecomastia was detected on the CT scan images one year after the initial diagnosis of the left pelvis cancer (A). Bilateral gynecomastia (encircled) was detected 18 months after the initial diagnosis on the axial CT scan image (B). Multiple lung metastases are pointed out by arrows.

Figure 3. Chest X-Ps. No obvious abnormalities were found (A). Multiple bilateral bulky lung metastases were detected 18 months after the initial diagnosis (B).

**Table 1.** Serum levels of hormones in the patient and our laboratory normal range

| Hormone (units)            | Serum level | Our laboratory normal range |
|----------------------------|-------------|-----------------------------|
| HCG (IU/mL)                | 142.4       | 0-3                         |
| Prolactin (ng/mL)          | 21.0        | 3.6-12.8                    |
| Estradiol (pg/mL)          | 189.1       | 19-51                       |
| Progesterone (ng/mL)       | 39.8        | 0-06                        |
| LH (U/mL)                  | <0.1ml      | 0.8-5.7                     |
| FSH (U/mL)                 | <0.1ml      | 2-8.3                       |
| Total testosterone (ng/dL) | 46.3        | 225-1039                    |
| Free testosterone (pg/mL)  | 1.4         | 35-155                      |

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