Urinary Excretion of Degradation Products of Prostacyclin and Thromboxane Is Increased in Patients with Gestational Choriocarcinoma

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ABSTRACT

Gestational choriocarcinoma metastasizes rapidly, in which process the vasoactive prostanoids may be significant. We therefore compared the urinary excretion of prostacyclin and thromboxane A2 (TxA2) metabolites in 19 women with gestational choriocarcinoma and 20 healthy age-matched women by assessing spot urine samples for 6-keto-prostaglandin F1α (6-keto-PGF1α) and 2,3-dinor-6-keto-prostaglandin F1α (2,3-dinor-6-keto-PGF1α) (degradation products of prostacyclin) as well as for thromboxane B2 (TxB2) and 2,3-dinor-TxB2 (degradation products of TxA2) by high-pressure liquid chromatography, followed by radioimmunoassay; the data were related to urinary creatinine concentration.

The urinary output of 6-keto-PGF1α [29.56 ± 7.0 versus 25.08 ± 3.91 ng/mmol creatinine (SE)] in patients with choriocarcinoma was normal, but that of 2,3-dinor-6-keto-PGF1α, in cancer patients was higher than in controls (24.44 ± 5.20 versus 14.84 ± 1.94, P < 0.02), as was that of TxB2 (22.72 ± 4.69 versus 9.69 ± 1.52, P < 0.001) and 2,3-dinor-TxB2 (114.21 ± 30.81 versus 51.81 ± 10.40, P < 0.01). The ratio of net prostacyclin output (6-keto-PGF1α, plus 2,3-dinor-6-keto-PGF1α) to the net TxA2 output (TxB2 plus 2,3-dinor-TxB2) in cancer patients (0.52 ± 0.1 (SE)] was lower (P < 0.03) than in the controls (0.83 ± 0.1), and in an inverse relation (r = −0.54, P < 0.05) to the scoring index of poor prognosis for the disease.

We conclude that the prostate excess in gestational trophoblastic disease, as evidenced for the first time in this study, may originate from choriocarcinoma cells, or may be a paraneoplastic phenomenon, and we conclude also that TxA2 excess may contribute to the tumor growth and/or formation of metastases.

INTRODUCTION

Gestational choriocarcinoma is characterized by strong metastatic capacity through blood circulation (1). Either the increased fibrinolytic activity (2, 3) or an altered prostanoid degradation products of the parent compounds, i.e., 6-keto-PGF1α and dinor-6-keto-PGF1α, in the case of PGI2, and TxB2 and 2.3-dinor-6-keto-prostaglandin F1α, 2.3-dinor-6-keto-prostaglandin F1α, 6-keto-prostaglandin F1α, 2,3-dinor-6-keto-prostaglandin F1α, we compared the urinary output of these metabolites in patients with gestational choriocarcinoma and in healthy control women.

PATIENTS AND METHODS

Thirty-nine Korean women were studied (Table 1), 19 with gestational choriocarcinoma at various clinical stages during the study (Table 1). Eight patients had received from 1 to 3 courses of various cytostatics (methotrexate, actinomycin D, etoposide, and vincristin), but during the study no drugs were given. They all excreted human chorionic gonadotropin into urine as evidence of the active state of the disease. The prognostic scoring index, taking into account clinical spread of the disease, antecedent pregnancy, tumor size, and human chorionic gonadotropin secretion (18), varied between 1 and 14 (mean, 8.5). Ten patients had the index 8 or more, indicating a high risk for the disease. Twenty healthy Korean women, who were comparable in regard to age, were studied as controls (Table 1). None of the study subjects had used any drugs known to affect prostanoid synthesis or metabolism within 7 days, and they did not use hormones or any intrauterine contraceptive device.

Spot urine samples were collected and stored frozen (−25°C) until assayed for 6-keto-PGF1α, dinor-6-keto-PGF1α, TxB2, and dinor-TxB2, by using high-pressure liquid chromatography, followed by radioimmunoassays; the details of the methods have been recently described elsewhere (19). The recovery of 6-keto-PGF1α, (50–200 pg/ml) added to the urine was 70.4 ± 10.3% (SD; n = 10), and that of 2,3-dinor-6-keto-PGF1α, 70.4 ± 5.8% (SD; n = 10). No correction for losses was made. The recovery of TxB2 (50–200 pg/ml) added to the urine was 61.3 ± 6.4%, and that of 2,3-dinor-TxB2, 70.4 ± 5.8% (SD; n = 10). No correction for losses was made. The intrasay coefficients of variation were less than 8%, and the interassay variations ranged from 10.4 to 14.1% for every metabolite.

Prostanoid excretion is expressed as ng/mmol creatinine, which was measured by using a routine laboratory method.

Due to the skewed distribution of urinary excretion of prostanoids, the data were transformed logarithmically, and the Student’s t test was used for calculating the significance of the differences between the cancer patients and the control population.

RESULTS

Choriocarcinoma patients excreted more dinor-6-keto-PGF1α [24.44 ± 5.20 versus 14.84 ± 1.94 ng/mmol creatinine (SE); 1.6-fold excess, P < 0.02], TxB2 (22.72 ± 4.69 versus 9.69 ± 1.52, 2.3-fold excess, P < 0.001), and dinor-TxB2 (114.21 ± 30.81 versus 51.81 ± 10.40, 2.2-fold excess, P < 0.014) than the controls, whereas the excretion of 6-keto-PGF1α in cancer patients was normal (29.56 ± 1.65 versus 25.08 ± 3.91) (Fig. 1).

The total excretion of TxA2 metabolites (TxB2 plus dinor-TxB2) of the cancer patients, 136.9 ± 40.0 ng/mmol creatinine, was higher (P = 0.007) than that of the controls (61.5 ± 11.7). The total excretion of PG12 metabolites (6-keto-PGF1α, plus dinor-6-keto-PGF1α), 54.6 ± 12.4 ng/mmol creatinine, did not differ from that of the controls (41.0 ± 5.7). Thus, the ratio of total PG12 output to total TxA2 output in cancer patients [0.53 ± 0.1 (SE)] was smaller (P < 0.03) than that of the controls (0.83 ± 0.1). Furthermore, the PG12/TxA2 ratio correlated
inversely ($r = -0.54$, $P < 0.05$) with the prognostic scoring index of each cancer patient (Fig. 2). Patients with cancer at Stage III–IV tended to excrete more PGI$_2$ ($62.2 \pm 17.0$ ng/mmol creatinine) and TxA$_2$ ($158.3 \pm 31.1$ ng/mmol creatinine) metabolites than did those with Stage I ($38.3 \pm 6.7$ ng/mmol creatinine and $114.6 \pm 41.9$ ng/mmol creatinine, respectively) ($P = 0.13–0.18$).

**DISCUSSION**

The dominance of TxA$_2$ over PGI$_2$ inside the cancer cell, or more generally in the body, favors the formation of platelet-cancer cell aggregates (9, 20–23), which then can easily attach to the vascular wall to form metastases (24, 25). Several malignancies produce excess amounts of PGI$_2$ and/or TxA$_2$ in vitro (26–30), or they are accompanied by elevated plasma or serum levels of PGI$_2$ and TxA$_2$ metabolites (31–35).

We have previously demonstrated an increased TxA$_2$ and increased or normal PGI$_2$ production with a TxA$_2$ dominance in breast cancer (36), ovarian cancer (37, 38), and endometrial cancer (39). In this study we assessed the production of PGI$_2$ and TxA$_2$ by patients with choriocarcinoma by measuring the urinary output of their degradation products. This is the best way available to evaluate the *in vivo* synthesis of these prostanoids (13–17). 6-Keto-PGF$_{1\alpha}$, and TxB$_2$ are assumed to originate mostly from the kidneys (40, 41), whereas dinor metabolites are considered to reflect the systemic PGI$_2$ and TxA$_2$ production (42–45).

Patients with choriocarcinoma excreted increased amounts of dinor-6-keto-PGF$_{1\alpha}$ and both TxA$_2$ metabolites, as shown now for the first time. This resembles the situation in patients with ovarian cancer (38), with the exception that patients with choriocarcinoma excreted normal amounts of 6-keto-PGF$_{1\alpha}$.

The increment of the excretion of TxA$_2$ metabolites was greater than that of PGI$_2$ metabolites, which resulted in a decreased PGI$_2$/TxA$_2$ ratio. This, and the inverse correlation between the ratio of PGI$_2$/TxA$_2$ metabolites and the prognostic scoring index strongly suggest the role of altered prostanoid production in the course of choriocarcinoma.

The origin of increased prostanoid production remains unclear. The source may be platelets or other circulating blood cells or various normal cells/tissues, or prostanoids may come directly from malignant trophoblastic cells. Interestingly, normal trophoblasts in tissue cultures produce both PGI$_2$ and TxA$_2$ (10, 11), and in molar pregnancies, which can be considered a premalignant form of choriocarcinoma, the concentrations of both PGI$_2$ and TxA$_2$ metabolites in intravesicular fluid are increased (12). Thus, the malignant trophoblasts themselves are likely one source of increased prostanoid production.

In conclusion, patients with gestational choriocarcinoma excrete increased amounts of dinor-6-keto-PGF$_{1\alpha}$, the main metabolite of extrarenal PGI$_2$, as well as clearly increased amounts of TxA$_2$ metabolites. This results in TxA$_2$ dominance, which may contribute to the metastatic potency of this malignancy.

**REFERENCES**


PROSTACYCLIN, THROMBOXANE, CHORIOCARCINOMA


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