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 metabolites in 19 women with gestational choriocarcinoma and 20 healthy age-matched women by assessing spot urine samples for 6-keto-prostaglandin F1a (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 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 prostanoid 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.

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 (SE); r = -0.54, P < 0.05] to the scoring index of poor prognosis for the disease.

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.
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 ± 17.0 ng/mmol creatinine) and TxA$_2$ (158.3 ± 31.1 ng/mmol creatinine) metabolites than did those with Stage I (38.3 ± 6.7 ng/mmol creatinine and 114.6 ± 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 intravascular 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**


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