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

Ansia A. Aitokallio-Tallberg, Jae K. Jung, Seung J. Kim, Lasse U. Viinikka, and R. Olavi Ylikorkala

Departments of Obstetrics and Gynecology [A. M. A-T., R. O. Y.] and Children’s Hospital [L. U. V.], University of Helsinki, SF-00290 Helsinki, Finland, and Department of Obstetrics and Gynecology, Catholic University Medical College, Kangnam St. Mary’s Hospital, Seoul, Korea [J. K. J. S. J. K.]

ABSTRACT

Gestational choriocarcinoma metastasizes rapidly, in which process the vasoactive prostanoids may be significant. Therefore we 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 F1a (6-keto-PGF1a) and 2,3-dinor-6-keto-prostaglandin F1a (2,3-dinor-6-keto-PGF1a) (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-PGF1a (29.56 ± 7.0 vs. 25.08 ± 3.91 ng/mmol creatinine (SE)) in patients with choriocarcinoma was normal, but that of 2,3-dinor-6-keto-PGF1a, in cancer patients was higher than in controls (24.44 ± 5.20 vs. 14.84 ± 1.94, P < 0.02), as was that of TxB2 (22.72 ± 4.69 vs. 9.69 ± 1.52, P < 0.001) and 2,3-dinor-TxB2 (114.21 ± 30.81 vs. 51.8 ± 10.40, P < 0.01). The ratio of net prostacyclin output (6-keto-PGF1a, plus 2,3-dinor-6-keto-PGF1a) 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.

INTRODUCTION

Gestational choriocarcinoma is characterized by strong metastatic capacity through blood circulation (1). Either the increased fibrinolytic activity (2, 3) or an altered prostanoid production of trophoblasts (4–7) may contribute to this property. Of the prostanoids, the vasodilatory and antiaggregatory effect of thromboxane A2; in vitro (10, 11), but the circulating concentration of their metabolites was not increased in patients with molar pregnancy, the benign type of gestational tumor (12). At present, production of PG12 and TxA2 in vivo is best assessed by measuring urinary output of the stable degradation products of the parent compounds, i.e., 6-keto-PGF1a and 2,3-dinor-6-keto-PGF1a, in the case of PG12, and TxB2 and 2,3-dinor-TxB2 in the case of TxA2 (13–17). Because no data exist on PG12 and TxA2 production in patients with choriocarcinoma, we compared the urinary output of these metabolites in patients with gestational choriocarcinoma and in healthy control women.

RESULTS

Choriocarcinoma patients excreted more 6-keto-PGF1a (24.44 ± 5.20 vs. 14.84 ± 1.94 ng/mmol creatinine (SE); 1.6-fold excess, P < 0.02), TxB2 (22.72 ± 4.69 vs. 9.69 ± 1.52; 2.3-fold excess, P < 0.001), and dinor-TxB2 (114.21 ± 30.81 vs. 51.8 ± 10.40; 2.2-fold excess, P < 0.014) than the controls, whereas the excretion of 6-keto-PGF1a in cancer patients was normal (29.56 ± 1.65 vs. 25.08 ± 3.91) (Fig. 1).

The total excretion of TXA2 metabolites (TxB2 plus 2,3-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-PGF1a, plus 2,3-dinor-6-keto-PGF1a), 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 PG1 \((62.2 \pm 17.0 \text{ ng/mmol creatinine})\) and TxA2 \((158.3 \pm 31.1 \text{ ng/mmol creatinine})\) metabolites than did those with Stage I \((38.3 \pm 6.7 \text{ ng/mmol creatinine} and 114.6 \pm 41.9 \text{ ng/mmol creatinine, respectively})\) \((P = 0.13–0.18)\).

**DISCUSSION**

The dominance of TxA2 over PG1 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 PG1 and/or TxA2 in vitro (26–30), or they are accompanied by elevated plasma or serum levels of PG1 and TxA2 metabolites (31–35).

We have previously demonstrated an increased TxA2 and increased or normal PG1 production with a TxA2 dominance in breast cancer (36), ovarian cancer (37, 38), and endometrial cancer (39). In this study we assessed the production of PG1 and TxA2 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-PGF1α and TxB2 are assumed to originate mostly from the kidneys (40, 41), whereas dinor metabolites are considered to reflect the systemic PG1 and TxA2 production (42–45).

Patients with choriocarcinoma excreted increased amounts of dinor-6-keto-PGF1α, and both TxA2 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-PGF1α.

The increment of the excretion of TxA2 metabolites was greater than that of PG1 metabolites, which resulted in a decreased PG1/TxA2 ratio. This, and the inverse correlation between the ratio of PG1/TxA2 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 PG1 and TxA2 (10, 11), and in molar pregnancies, which can be considered a premalignant form of choriocarcinoma, the concentrations of both PG1 and TxA2 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-PGF1α, the main metabolite of extrarenal PG1, as well as clearly increased amounts of TxA2 metabolites. This results in TxA2 dominance, which may contribute to the metastatic potency of this malignancy.

**REFERENCES**


PROSTACYCLIN, THROMBOXANE, CHORIOCARCINOMA


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