The Value of Platelet-derived Endothelial Cell Growth Factor as a Novel Predictor of Advancement of Uterine Cervical Cancers

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ABSTRACT

Serum platelet-derived endothelial cell growth factor (PD-ECGF) in patients with uterine cervical cancers revealed a significantly positive correlation with uterine stage and tumor size and with the advancement indicators lymph node metastasis, parametral involvement, and vessel permeation in both squamous cell carcinomas and adenocarcinomas. The prognosis of the patients with high serum PD-ECGF was extremely poor, whereas the 36-month survival rate of the other patients with low serum PD-ECGF was 81.3% in squamous cell carcinomas and 80.0% in adenocarcinomas. Our data indicate that serum PD-ECGF levels reflect the status of advancement of uterine cervical cancers and thus may be recognized as a novel tumor marker for both squamous cell carcinomas and adenocarcinomas of the uterine cervix.

INTRODUCTION

PD-ECGF was cloned as a novel angiogenic factor (M, 45,000 polypeptide) from human platelets (1). Thereafter, PD-ECGF was completely identified with TP (2, 3). PD-ECGF/TP does not stimulate the growth of endothelial cells but chemotaxis of them and induces angiogenesis in vivo with the activation of TP as an enzyme (4, 5). PD-ECGF is expressed in lymph nodes, peripheral lymphocytes, spleen, lung, liver, and placenta among normal tissues. Among solid tumors, PD-ECGF is expressed in malignant gliomas, thyroid tumors, cancers of the breast, esophagus, stomach, colon, pancreas, gallbladder, kidney, bladder, ovary, uterine cervix, and lung (6).

PD-ECGF action on the advancement of female genital tract diseases can be gleaned from the following. PD-ECGF was up-regulated in normal uterine endometrium after ovulation (7), whereas steroid regulation of PD-ECGF was deficient in ovarian endometriosis during the menstrual cycle (8). In uterine endometrial cancers, PD-ECGF was dominantly expressed in interstitial cells and contributed to myometrial invasion of the cancer cells and tumor growth in the early stage (9). In ovarian cancers, PD-ECGF was remarkably highly expressed in some ovarian cancers; however, its levels did not correlate with patient prognosis (10). In uterine cervical cancers, PD-ECGF was dominantly expressed in interstitial cells, and its levels correlated with microvessel density and patient prognosis (11).

Among female genital tract cancers, PD-ECGF in the primary tumor of uterine cervical cancers is recognized as a prognostic indicator. On the other hand, the presence of lymph node metastasis, recognized as the most common metastatic lesion, is critical to patient management, especially the monitoring of tumor recurrence and therapeutic response (17–25). The aim of this study was to investigate whether serum PD-ECGF in comparison with serum SCC can be used as a tumor marker of uterine cervical cancers.

MATERIALS AND METHODS

Patients and Specimens. Consent for the following studies was obtained from all patients and the Research Committee for Human Subjects, Gifu University School of Medicine. One hundred twenty patients ranging from 31 to 74 years of age and 20 volunteers ranging from 31 to 74 years of age provided peripheral blood at the Department of Obstetrics and Gynecology, Gifu University School of Medicine, between January 1992 and July 1996.

PD-ECGF and SCC Antigen Levels. Serum PD-ECGF and SCC antigen levels were determined by the sandwich enzyme immunoassay of the modified Nishida’s method (27) and by enzyme immunoassay using an IMX SCC kit (Dinabot, Tokyo, Japan), respectively, in triplicate.

Statistics. Survival curves were calculated using the Kaplan-Meier method and analyzed by the log-rank test. Statistical analysis was performed with Student’s t test. Differences were considered significant when P < 0.05.

RESULTS

Serum SCC levels were significantly (P < 0.05) higher in 72 SCCs (3.37 ± 2.97 ng/ml) compared with 48 adenocarcinomas of the uterine cervix (0.69 ± 0.15 ng/ml) and increased with increasing disease stage in SCCs but not in adenocarcinomas (Fig. 1). There was no significant difference in serum PD-ECGF levels between SCCs and adenocarcinomas of the uterine cervix and levels increased with increasing disease stage, regardless of histopathological type (Fig. 1).

To analyze the correlation between tumor size and serum SCC or PD-ECGF level, the patients with stage Ib and II uterine cervical cancers were selected. There was a significant positive correlation between tumor size and serum SCC level in SCCs (SCC = 0.0540 × tumor size + 0.480; r = 0.839; P < 0.01), but not in adenocarcinomas, as shown in Fig. 2.

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1 The abbreviations used are: PD-ECGF, platelet-derived endothelial cell growth factor; TP, thymidine phosphorylase; SCC, squamous cell carcinoma; LN meta, lymph node metastases; PI, parametrial involvement; VP, vessel permeation.

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In SCC patients, serum SCC levels were significantly ($P < 0.05$) higher in 36 patients with positive pelvic LN meta compared with 36 patients with negative LN meta (Fig. 3a), in 44 patients with positive PI compared with 28 patients with negative PI (Fig. 3b), and in 41 patients with positive VP compared with 31 patients with negative VP (Fig. 3c). There were no such differences in adenocarcinoma patients (Fig. 3). Regardless of histopathological type, serum PD-ECGF levels were significantly ($P < 0.05$) higher in 63 patients with positive LN meta compared with 57 patients with negative LN meta (Fig. 3a), in 74 patients with positive PI compared with 46 patients with negative PI (Fig. 3b), and in 69 patients with positive VP compared with 51 patients with negative VP (Fig. 3c).

To analyze patient prognosis related to serum SCC and PD-ECGF levels, the patients with stage II uterine cervical cancer after curative resection were selected. The prognosis of SCC patients with high serum SCC was very poor, whereas the 36-month survival rate of the other SCC patients with low serum SCC was 81.3%. There was no significant difference in the prognosis of adenocarcinoma patients.
Furthermore, the prognosis of the patients with high serum PD-ECGF and VP in both SCCs and adenocarcinomas of the uterine cervix. and with the advancement indicators lymph node metastasis, PI, and VP. The prognosis of the patients with high serum PD-ECGF was extremely poor, regardless of histopathological type. Our data indicate that serum PD-ECGF levels reflect the status of advancement of uterine cervical cancers and thus may be recognized as a novel tumor marker for both SCCs and adenocarcinomas of the uterine cervix. Additionally, the levels of PD-ECGF in the serum are only 1,000- to 10,000-fold lower than those in uterine cervical cancer tissues we determined previously (11, 16).

**DISCUSSION**

SCC has been recognized as a very reliable marker for tumor advancement including nodal metastasis of SCCs of the uterine cervix (24, 25). In the present study, serum SCC levels in patients with SCC of the cervix revealed a significantly positive correlation with clinical stage and tumor size and with the advancement indicators lymph node metastasis, PI, and VP. The prognosis of the patients with high serum SCC was very poor in SCCs. On the other hand, serum SCC in adenocarcinomas was always low, and the levels revealed no positive correlation with clinical stage or tumor size, nor with the advancement indicators lymph node metastasis, PI, and VP. Additionally SCC levels had no correlation with adenocarcinoma patients' prognoses. Our findings reconfirm that SCC is an excellent tumor marker for SCC of the cervix.

Researchers have attempted to use CA125 as a tumor marker for adenocarcinoma of the cervix. Expression of CA125 was diffusely positive in normal endocervical glands, whereas the expression was significantly decreased in minimal deviation adenocarcinomas of the cervix (28). Conversely, elevated serum CA125 was detected with large variation of positive ratio in adenocarcinomas of the cervix (29, 30). Therefore, CA125 seems not to be a reliable tumor marker for the advancement of uterine cervical cancers.

In the present study, the levels of serum PD-ECGF revealed a significantly positive correlation with clinical stage and tumor size, and with the advancement indicators lymph node metastasis, PI, and VP in both SCCs and adenocarcinomas of the uterine cervix. Furthermore, the prognosis of the patients with high serum PD-ECGF was extremely poor, regardless of histopathological type. Our data indicate that serum PD-ECGF levels reflect the status of advancement of uterine cervical cancers and thus may be recognized as a novel tumor marker for both SCCs and adenocarcinomas of the uterine cervix. Additionally, the levels of PD-ECGF in the serum are only 1,000- to 10,000-fold lower than those in uterine cervical cancer tissues we determined previously (11, 16).

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