Glycodelin in Ovarian Serous Carcinoma: Association with Differentiation and Survival

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ABSTRACT

Ovarian cancer consists of many subtypes, serous carcinoma being the most common of them. In addition to the histopathological subtype, grading, clinical staging, and the amount of residual tumor, a great number of putative prognostic markers have been introduced. This study addresses in ovarian serous carcinoma the role of glycodelin, the major progesterone-regulated lipocalin protein of the reproductive axis with diverse actions in cell recognition and differentiation. Glycodelin expression was determined by immunohistochemistry of tissue microarrays in ovarian serous carcinomas from 460 patients, and the results were analyzed with respect to progesterone receptor subtype A (PRA) and progesterone receptor subtype B (PRB), clinical parameters, and survival. Glycodelin was localized to the cytoplasm of tumor cells, whereas vascular endothelium in tumor tissue was glycodelin-negative. Glycodelin expression was more frequent in well-differentiated (grade I, 79%) than in poorly differentiated carcinomas (grade III, 51%; P < 0.0001), and it was also more frequent in early-stage compared with advanced-stage carcinomas (P = 0.002). Nuclear PRA and PRB were often coexpressed with cytoplasmic glycodelin. Although this was not consistent in all tumors, there was a positive correlation between the presence of glycodelin and PRs in the tumor (P < 0.02), but not between the presence of, or the absence of, glycodelin in tumor and the CA-125 serum concentration. Although in multivariate analysis glycodelin was not an independent variable, the patients with glycodelin-expressing tumors showed a higher 5-year overall survival compared with those with glycodelin-negative tumors (55 versus 39%; P = 0.0001; hazard ratio in univariate analysis, 0.57; confidence interval, 0.44–0.74). This difference was notable in patients with grade I tumors and stage III disease. In the latter group, the 10-year survival probability of patients with glycodelin-positive tumors was more than twice as high as that in women with glycodelin-negative tumors. This was also found within well-defined clinical categories, e.g., stage III/grade II and stage III/grade III carcinomas, in which patients with glycodelin-positive tumors carried significantly better 10-year overall survival compared with those with glycodelin-negative tumors. It is concluded that, in ovarian serous carcinoma, glycodelin expression portends better prognosis, probably because of its differentiation-related disposition.

INTRODUCTION

Ovarian cancer is the leading cause of death in patients with gynecological cancer in the Western World. Radical surgery is the cornerstone of effective treatment, essential for accurate staging, histological classification, grading and risk estimation, and adjuvant chemotherapy (1). Whereas clinical stage and histological grade are the gold standards for clinical management, a great number of diagnostic and prognostic indicators have been explored, from analyses of individual proteins, chromosomes, and genes to microarray technology, proteomics, and bioinformatics (2–12). Glycodelin is the major lipocalin protein of the reproductive axis, with diverse actions in cell recognition and differentiation (13). Its relationship with epithelial differentiation is well established in the normal endometrium in which temporal glycodelin expression is progesterone-regulated (14–18), as well as in cultured endometrial and breast carcinoma cell lines (14, 19). Glycodelin is involved in cell recognition in reproductive and immune systems. It inhibits gamete interaction (20) and immune reactions (21–23). Transfection experiments suggest that glycodelin plays a role as a cellular morphogen that induces differentiation (19).

A previous report on ovarian cyst fluids suggests higher levels of glycodelin in benign and borderline serous cysts compared with mucinous cysts and those related to advanced carcinoma (24).

In view of its association with differentiation and progesterone action we studied glycodelin expression in archival tumor tissue specimens removed at primary surgery from 460 patients with ovarian serous carcinoma, paying special attention to its localization in tumor tissue and correlations with PRs, histological grade, clinical stage, serum CA-125 concentration, and survival of the patients.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board of the Department of Obstetrics and Gynecology, Helsinki University Central Hospital. Tissue specimens from the patients treated in 1964–1999 for ovarian serous carcinoma were identified from the Helsinki University Central Hospital records. Clinical patient information was extracted from the records, and additional survival data were provided by the Finnish Population Register Center. The patients lacking data on primary treatment and survival, or with inadequate tissue specimens, were not included, leaving 460 patients for the analysis. At the time of diagnosis, the mean age of the patients was 56.6 ± 13.2 years (mean ± SD; median, 57.0 years; range, 18–88 years).

During the 26-year period new treatment regimens were adopted after advances in the field, including cisplatin- and paclitaxel-based chemotherapy and more radical surgery. The effects of storage of the specimens on glycodelin expression and the impact of new treatments on disease survival were addressed by dividing the material into two temporally successive groups according to diagnosis, the first group including 230 patients treated in 1964–1988 and the remaining group including 230 subsequent patients treated in 1988–1999. Cisplatin became available in late 1979, and the material was also analyzed with respect to the period before (n = 113) and after cisplatin (n = 347). Furthermore, results for the patients treated before paclitaxel, until 1996 (n = 363), and those treated with paclitaxel (n = 97), were compared with each other. Treatment modalities or socioeconomic status did not affect selection of the patients because, according to the National Health Care Policy, all of the patients were treated at public hospitals of the Helsinki University Central Hospital catchment area at a nominal charge per day, irrespective of the mode of treatment, and all those with adequate records and archival tumor specimens were included in the study.

The samples were obtained at primary surgery before chemotherapy or other treatment. Histopathological grading and clinical staging were done for all of the tumors according to established criteria (Table 1). Disease-specific survival time was calculated from the date of histologically verified diagnosis to death.
from ovarian carcinoma. The patients who had died from intercurrent causes or who were lost to follow-up were censored. The median survival time of the patients was 4.9 years.

**Construction of Tissue Microarrays**

The tissue microarrays were carried out as described previously (25). Briefly, 5-μm sections of formalin-fixed, paraffin-embedded tumor tissues were stained with H&E to select representative areas for biopsies. Core tissue specimens (diameter, 0.8 mm) were then taken from these areas of donor paraffin blocks and precisely arrayed into a new recipient paraffin block with a custom-built instrument (Beecher Instrument, Silver Spring, MD). Tissue specimens from ovarian serous carcinomas and normal ovaries were arranged in six recipient paraffin blocks. Four core-tissue biopsies were obtained from each specimen. The presence of malignant tissue in the array specimens was confirmed from H&E-stained sections.

**Immunohistochemistry**

**Glycodelin.** The immunohistochemical analyses of glycodelin were carried out in Helsinki by using the immunoperoxidase method (26). Briefly, 5-μm-thick sections were cut from each array block, deparaffinized, rehydrated, and subjected to microwave heat treatment to enhance immunoreactivity. Rabbit (no. 1) antiglycodelin IgG was used as the first antibody (2.5 μg/ml), and preimmune IgG from the same rabbit was used as a negative control. The second antibody was biotinylated porcine antirabbit immunoglobulin (DAKO A/S, Glostrup, Denmark). Immunostaining was carried out with the use of Vectastain ABC kit (Vector Laboratories, Burlingame, CA), and with 3-amino-9-ethylcarbazole as a substrate. The sections were counterstained with hematoxylin. Specificity of staining was also controlled by absorbing the glycodelin antibody with purified glycodelin (16 μg/ml, overnight at +4°C). No staining was observed in the control experiments.

Glycodelin staining was first scored from 0 to 2 (0, no staining; 1, weak staining; 2, strong staining). For additional statistical analyses, the material was divided into two groups: glycodelin-positive and glycodelin-negative.

**PRs.** The immunohistochemical analyses of PRA3 and PRB were carried out at Dr. Jan-Åke Gustafson’s laboratory in Stockholm. Primary antibodies, generated in mice, were purchased from Novocastra (Newcastle upon Tyne, United Kingdom). PGR-312 antibody recognizes PRA, and PGR-AB-SAN27 antibody recognizes PRB (27).

Paraffin sections (4 μm) were dewaxed in xylene and rehydrated through graded ethanol to water. Endogenous peroxidase was blocked by incubation for 30 min in a solution of 1% hydrogen peroxide, and antigen presentation was enhanced by microwaving the sections in 0.01 M citrate buffer (pH 6.0), for 20 min at 800 W. The tissue sections were incubated for 1 h at +4°C with normal goat serum diluted 1:10 in PBS. Primary antibodies were diluted 1:100 in PBS, containing 3% BSA, and were incubated on the sections overnight at +4°C. For negative primary antibody controls, the primary antibody was replaced with PBS alone. After washing, the sections were incubated with biotinylated goat antirabbit immunoglobulin (1:200 dilution; Vector Laboratories Inc.) for 2 h at room temperature, followed by washing in PBS and incubation in avidin-biotin-HRP for 1 h (Vectastain ABC-kit; Vector Laboratories Inc.). After thorough washing in PBS, the sections were developed with 3,3’-diaminobenzidine tetrahydrochloride (DAKO A/S, Glostrup, Denmark), slightly counterstained with Mayer’s hematoxylin, and dehydrated with graded ethanol concentrations, followed by exposure to xylene and by mounting. The expression of the receptors was regarded as positive when the cells showed nuclear brown staining.

**Double Stainings for Glycodelin and PRA/PRB.** The stainings were carried out on 66 tumors in Helsinki using the PicTure-Double staining kit (Zymed Laboratories Inc., San Francisco, CA) according to the manufacturer’s instructions. Briefly, the sections were deparaffinized, rehydrated, and subjected to microwave treatment to enhance immunoreactivity. Endogenous peroxidase activity was blocked with perhydrol in methanol. Nonspecific binding of secondary antibodies was eliminated by the blocking solution provided in the kit. Primary antibodies against glycodelin and PRA and PRB were the same as described above. The PR antibodies were diluted 1:300, and anti-glycodelin IgG was used at a concentration of 2.5 μg/ml in PBS. The first antibodies were incubated concomitantly on tissue sections for 4.5 h at room temperature. Two secondary antibodies were used according to the kit instructions, an HRP-conjugated goat antirabbit antibody for the PRs and an alkaline phosphatase-conjugated goat antirabbit antibody for glycodelin. Substrate- chromogens for HRP and alkaline phosphatase were 3,3’-diaminobenzidine tetrahydrochloride and Fast-Red, respectively. The sections were counterstained with hematoxylin. A positive reaction for PRA or PRB appeared as brown staining in the nucleus, and glycodelin appeared as red staining in the cytoplasm.

**CA-125 Measurement**

Serum for CA-125 measurement was available for 238 patients. An immunoradiometric assay (Centocor, Malvern, PA) was used until the end of year 1995. After that, the CA-125 levels were determined by an immunoenzymatic assay (Immuno1, Bayer, Tarrytown, NY). A cutoff value of 35 kU/liter was used. At this level and higher, the two methods gave similar results.

**Statistical Analyses**

Survival probabilities were calculated according to the Kaplan-Meier method. Survival curves between groups with different glycodelin staining were compared by the log-rank test. Pearson’s χ² test and Mantel-Haenzel’s χ² tests were used to test associations between categorical variables. Student’s t test and the Mann-Whitney U test were used for significance testing of parametric and nonparametric data, respectively. Binary logistic regression was used for multivariate modeling of the correlation between explanatory variables and the glycodelin staining status. Cox proportional hazards model was used to create a multivariate survival model, in which glycodelin staining status (glycodelin-positive or negative), tumor grade (grades I, II, and III), FIGO (Fédération Internationale des Gynaecologistes) stage (stages I, II, III, and IV), tumor size (≤10 cm or >10 cm), residual tumor size (<1 cm or >1 cm), ascites at primary operation (presence or absence) and time of diagnosis were entered as categorical variables, and age as a continuous variable. Backward stepwise method was used to select important variables. For the estimations of differences in 5- and 10-year survival between glycodelin-positive and -negative groups, SIEs and Ps were calculated for the differences of the survival probabilities. P < 0.05 was considered statistically significant, and all of the tests were performed two-tailed. The analyses were performed using SPSS 10.07 for Windows (SPSS Inc., Chicago, IL).

**RESULTS**

**Glycodelin Expression.** The flat surface epithelium of normal postmenopausal ovary (n = 5) was glycodelin negative in all but one case, and metaplastic cuboidal and columnar cells on the ovarian surface and in the inclusion invaginations and cysts, stained weakly positive for glycodelin. Glycodelin immunostaining was available for 460 patients with ovarian serous carcinoma in which glycodelin was localized in the cytoplasm of malignant epithelial cells, whereas vascular endothelium in tumor tissue was glycodelin negative (Fig. 1). Sixty-five % (n = 301) of the tumors were glycodelin positive and 35% (n = 159) were glycodelin negative. In the glycodelin-positive group, 71% of the tumors (n = 214) showed weak and 29% (n = 87) showed strong staining.

**PRA and PRB Expression Relative to Glycodelin in Malignant Tissue.** In the total of 460 ovarian serous carcinomas, PRA was found in 33% and PRB in 14% of the tumors. When present, both receptors were localized to nuclei of the malignant cells. PRA was present in 37% of the glycodelin-positive and 26% of the glycodelin-negative tumors (P < 0.02), and PRB was present in 17% and 8% of the tumors, respectively (P < 0.02). All of the PRB-positive tumors also stained for PRA, whereas only 44% of the PRA-positive specimens were PRB-positive. In double staining (n = 66), glycodelin and PRA/PRB expression were seen in the same as well as in different cells (Fig. 1, F–I).

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3 The abbreviations used are: PRA, progesterone receptor subtype A; PRB, progesterone receptor subtype B; CI, confidence interval; HRP, horseradish peroxidase; HR, hazard ratio; Gp, glycodelin peptide.
Glycodelin Expression and Clinical Parameters. Glycodelin expression correlated with tumor grade. Percentages of glycodelin-positive tumors in the whole material were: grade I, 79%; grade II, 63%; grade III, 51% (Fig. 2). Strong glycodelin staining was less frequent among the patients with grade II or III disease compared with those with grade I tumors ($P < 0.0001$). A similar decreasing trend of glycodelin expression was observed in tumors with advancing clinical stage ($P = 0.002$; Fig. 2). When both grade and stage were included in the logistic regression model to predict glycodelin expression, grade remained the significant variable ($P < 0.0001$).

No difference was observed in initial tumor size, age, or presence of ascites between glycodelin-positive and -negative subjects. After primary debulking surgery, residual tumors were more frequently ($P < 0.001$) small (<1 cm) among glycodelin-positive [148 (59%) of 250] than among glycodelin-negative patients [54 (41%) of 132] patients.

Glycodelin Expression Is Related to Better Survival. Overall, the patients with glycodelin-positive tumors had a higher survival rate compared with glycodelin-negative subjects (Table 1; Figs. 3 and 4). This difference was notable for grade I tumors ($P = 0.0196$) or stage III disease ($P = 0.0015$), in which the 10-year survival probability of the patients with glycodelin-positive tumors was more than twice as high as that of the patients with glycodelin-negative tumors ($P < 0.001$; Table 1; Fig. 4). Within certain well-defined clinical groups belonging to the same clinical stage and differentiation grade category, the patients with glycodelin-positive carcinoma had, at certain time points, a better overall survival than those with glycodelin-negative carcinoma. This was seen in the women with stage II/grade III carcinoma at 5 years ($P = 0.003$), stage III/grade II carcinoma at 10 years ($P = 0.0001$), stage III/grade III carcinoma at 10 years ($P = 0.04$), and stage IV/grade III carcinoma at 5 years ($P = 0.02$).

Among all the patients, survival in either weakly or strongly staining groups was better than that in the group with no glycodelin staining ($P < 0.001$), whereas no difference was found in the survival between weakly and strongly staining groups. Therefore, additional analyses were performed between the glycodelin-positive and -negative groups, disregarding staining intensity. A HR of 0.57 (CI, 0.44–0.74) was obtained for the patients with glycodelin-positive tumors, when the glycodelin expression status was entered into the univariate Cox multiple hazards model. In the backwards stepwise selection of multiple variables, glycodelin was not identified as an independent variable.

Comparison between the first 230 patients, treated in 1964–1988,
and the subsequent 230 patients, treated in 1988–1999, showed no significant difference in glycodelin staining intensity between the two groups. Staining was weak in 110 (69.6%) of 158 tumors and strong in 48 (30.4%) of 158 tumors in the earlier group and weak in 104 (72.7%) of 143 and strong in 39 (27.3%) of 143 in the latter period (Pearson χ² test, \( P = 0.553 \)). As with the intensity, there was no significant difference in the relative amount of glycodelin-positive tumors between the two groups (158 of 230 versus 143 of 230, respectively; \( \chi^2 \) test, \( P = 0.141 \)). In both of the groups, survival of the patients with glycodelin-positive tumors was higher than those with the glycodelin-negative tumors (log-rank test, \( P = 0.0001 \) and \( P = 0.0117 \), respectively). In the backwads stepwise selection of multiple variables, the time of diagnosis remained an independent prognostic factor (HR, 0.63; CI, 0.46–0.85; \( P = 0.003 \)), showing that in the latter group the risk of death was significantly smaller.

Regarding treatments that took place before or after cisplatin, no difference was found in the intensity of glycodelin staining in either group. Among glycodelin-expressing tumors treated before cisplatin, staining was weak in 57 (70.4%) of 81 and strong in 24 (29.6%) of 81 tumors, and during cisplatin, staining was weak in 157 (71.4%) of 220 and strong in 63 (28.6%) of 220 tumors (Pearson \( \chi^2 \) test, \( P = 0.866 \)). Using the log-rank test, higher survival remained significant for the patients with glycodelin-positive tumors, both before and after cisplatin (\( P = 0.0113 \) and \( P < 0.0001 \), respectively). During the cisplatin era, survival was significantly improved (multivariate analysis, HR, 0.54; CI, 0.38–0.77; \( P < 0.001 \)).

Glycodelin-positive tumors were less frequent after adoption of paclitaxel (53 of 97 or 54.6%) than before it (248 of 363 or 68.3%; Pearson \( \chi^2 \) test, \( P = 0.012 \)), whereas no significant difference was observed in the intensity of staining. Before paclitaxel, glycodelin-positive staining was weak in 178 (71.8%) of 248 and strong in 70 (28.2%) of 248 tumors, and during paclitaxel the staining was weak in 36 (67.9%) of 53 and strong in 17 (32.1%) of 53 tumors (Pearson \( \chi^2 \) test, \( P = 0.575 \)). Unlike in the other groups, in the paclitaxel group (\( n = 97 \)), no difference in survival was found between glycodelin-positive and -negative tumors (\( P = 0.3498 \), whereas the difference was highly significant in the group before paclitaxel (\( n = 363; P < 0.0001 \)). In the multivariate model, time of diagnosis was not an independent prognostic factor in the paclitaxel group, probably because the number of patients was small.

Despite improved diagnostic facilities, relatively more advanced-stage carcinomas were referred for treatment at the Helsinki University Hospital during the period of more-advanced chemotherapy. This is illustrated by the mean stage of disease on admission of the patients, as divided into various treatment categories. Thus, in the first group of 230 treated patients treated until 1988, the mean figure for stage was 2.41 compared with 2.71 in the latter group of 230 patients (the Mann-Whitney test, \( P = 0.00035 \)). The same trend was seen with respect to the adoption of cisplatin (2.35 versus 2.63; \( P = 0.005 \)) and paclitaxel treatments (2.5 versus 2.78; \( P = 0.007 \)).

**CA-125 Levels and Glycodelin Expression.** There was no correlation between serum CA-125 levels and glycodelin immunostaining status in tumors (\( P > 0.05 \), for all).

**DISCUSSION**

In the normal postmenopausal ovary, glycodelin was not commonly expressed. This is different from the fertile-phase ovary in which glycodelin is present in various cell types, notably luteinized granulosa cells (26, 28). The reasons for this difference may be related to decreased hormonal activity in the postmenopausal ovary.

In ovarian carcinoma, glycodelin was localized in the cytoplasm of malignant cells, not in the vascular endothelium of tumor tissues. This finding is at variance with the recent studies using anti-Gp antibodies, which react with vascular endothelial cells (29, 30). Importantly, Gp immunoreactivity in umbilical cord vein endothelial cells appears to result from uptake rather than synthesis, because little or no glycodelin message is detectable in the same cells (30). This observation is similar to a recent finding of glycodelin protein but not the corresponding mRNA in ovarian cumulus cells (28). Contrary to these observations, we have previously found both glycodelin mRNA and glycodelin protein to be present in ovarian serous carcinoma tissue.

### Table 1 Five- and 10-year overall survival rates of patients with glycodelin (Gd)-positive and -negative ovarian serous carcinoma

<table>
<thead>
<tr>
<th>Disease</th>
<th>n</th>
<th>5-year overall survival (%)</th>
<th>95% CI (%)</th>
<th>10-year overall survival (%)</th>
<th>95% CI (%)</th>
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<tr>
<td>All</td>
<td>460</td>
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<td>40</td>
<td>35–46</td>
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<tr>
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<td>50–61</td>
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<td>34–45</td>
<td>26b</td>
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<tr>
<td>Stage I</td>
<td>All</td>
<td>97</td>
<td>93–99</td>
<td>83</td>
<td>74–92</td>
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<tr>
<td>Gd-ve</td>
<td>74</td>
<td>70c</td>
<td>65–76</td>
<td>83c</td>
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<tr>
<td>Gd-ve</td>
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<td>76–86</td>
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<tr>
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<td>Gd-ve</td>
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<tr>
<td>Stage IV</td>
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\( a P < 0.001 \)

\( b P < 0.0001 \)

\( c ns, not significant \)

\( d P < 0.01 \)

\( e P < 0.05 \)
providing evidence for synthesis (26). Therefore, \textit{in situ} hybridization of glycodelin mRNA was not repeated in this study. Irrespective of the differences in immunolocalization results, immunological mimicry of the two types of antibodies is obvious, and the identity of anti-Gp antibodies with the conformational anti-glycodelin antibodies used in this study remains to be investigated to reconcile the differentiative (glycodelin) versus angiogenic (Gp) associations (14, 29).

In the total material, 65% of tumors contained glycodelin, the expression of which was more common in well-differentiated carcinomas that showed papillary or glandular structures. One would have expected that the intensity of immunohistochemical staining would be decreased during long storage of tissue specimens as in this study, but this was found not to be the case, perhaps because glycodelin is stable and well protected by its high carbohydrate content. The proportion of glycodelin-positive and -negative tumors remained roughly similar over the long period of time, except that, after the adoption of paclitaxel treatment, the frequency of glycodelin-positive tumors was lower than in the tumors treated before paclitaxel. This may be related to the increased proportion of advanced-stage carcinomas referred for treatment as the new treatment modalities became available in the tertiary referral centers.

Changes in tumor grade must be secondary to genetic and biochemical changes that have taken place in the cells undergoing neoplastic transformation. Contact with the basement membrane regulates epithelial cell growth and normal organization (31). Both the basement membrane and the stromal cells are required in this process so that, before its emergence, the tumorigenic phenotype must overcome the suppressive effects of the surrounding microenvironment (32). Loss of the basement membrane components collagen IV and laminin may be an early event in the preneoplastic transformation of ovarian surface epithelium (31). Importance of the microenvironment has been demonstrated by the experiments in which endometrial adenocarcinoma cells resume glycodelin secretion and concomitant differentiation when cocultured in the presence of normal stromal cells and basement membrane components (14). Further evidence for the differentiative association of glycodelin comes from experiments on breast cancer cells in which transfection of glycodelin cDNA is followed by retarded growth, formation of gland-like structures, and expression of epithelial cytokeratins (19), suggesting that glycodelin is not only a marker of epithelial differentiation but may play a fundamental role in glandular morphogenesis. Interestingly, the induction of glandularity during the early stages of ovarian carcinoma development appears to produce a microenvironment that has much in common with the normal mammary gland (32). Compared with well-differentiated serous carcinomas, reduced glycodelin expression in poorly differentiated ovarian cancer may result from dedifferentiation or loss of genetic material. Genetic changes, both gains and losses, are frequent in ovarian tumors (33) and include a high frequency of deletions at chromosome 9 (34), which harbors the glycodelin gene (35).

Glycodelin and PRA/PRB were frequently found in the same malignant cells, but this was not always the case. It is difficult to claim functional association between the two, although this cannot be ruled
out in view of the fact that glycodelin gene consists of four putative glucocorticoid/progesterone elements (18). Both PRA and PRB function as ligand-activated transcription factors, but the two isoforms have different functional characteristics (36, 37). Ligand-activated PRA and PRB both induce glycodelin expression in endometrial adenocarcinoma cells in vitro (17). In this study, we observed a positive correlation between glycodelin and PRA and PRB in ovarian cancer, showing that both types of receptors appear in these glycodelin-expressing cancers, even in the same cells. However, because many glycodelin-positive ovarian carcinomas were PR negative, regulatory factors other than progesterone must also be involved in glycodelin expression.

Glycodelin expression had no relation to initial tumor size, whereas glycodelin-expressing residual tumors were smaller. Because this was a retrospective observation, interpretation of this observation remains speculative. A simple interpretation would be better operability of glycodelin-expressing tumors, which is also supported by the survival data.

Given the reported differentiative association of glycodelin (14, 16, 19), it is not surprising that the patients with glycodelin-expressing tumors had better survival than those with glycodelin-negative tumors. This was specifically noted in patients with histological grade I and clinical stage III cancer. The reason that the trends are best seen in grade I and stage III tumors is probably because these groups were large enough to have adequate power to detect the differences as opposed to some other stages and grades that were broken down into smaller numbers and, therefore, were much less likely to have any differences detected. It is not yet known whether glycodelin expression, which emerged as an independent variable, is primary or secondary to the changes in tumor grade. The association of tumor glycodelin with better survival at certain time points was seen even in patients with the same tumor grade and clinical stage. It is, therefore, concluded that, although not an independent variable in ovarian cancer, glycodelin expression in tumor tissue portends better prognosis, probably because of its differentiation-associated propensity.

REFERENCES


Fig. 4. Cumulative survival of patients with glycodelin-positive versus glycodelin-negative tumors stratified by clinical stage. Gd +ve, glycodelin positive; Gd -ve, glycodelin negative.


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