Anti-Mesothelin Antibodies and Circulating Mesothelin Relate to the Clinical State in Ovarian Cancer Patients

Ingegerd Hellstrom,1 Eitan Friedman,2,3,4 Thorsten Verch,5 Yi Yang,1 Jacob Korach,4 Jade Jaffar,1 Elizabeth Swisher,6 Boxin Zhang,6 Gilad Ben-Baruch,4 Marcus C.B. Tan,7 Peter Goedegebuure,7 and Karl Erik Hellstrom1

1Department of Pathology, Harborview Medical Center, Seattle, Washington; 2Danek Gertner Institute of Genetics, Susanne Levy Gertner Oncogenetics Unit, and 3Department of Gynecology, Sheba Medical Center, Tel Hashomer, Israel; 4Department of Gynecology, University of Washington, Seattle, Washington; and 5Department of Surgery, Washington University, St. Louis, Missouri

Abstract

Most human ovarian carcinomas express mesothelin, which is shed as a diagnostically useful biomarker. We applied an ELISA to measure antibodies to native mesothelin in serum from a series of patients with divergent clinical outcomes. The level of anti-mesothelin antibodies determined as OD_{450 nm} and referred to as absorption units (AU) for 1:20 diluted serum was higher in patients who remained disease-free after therapy [no evidence of disease (NED); n = 14] than in patients whose disease recurred [clinical evidence of disease (CED); n = 21; P < 0.01]. Applying AU ≥ 0.5 at a serum dilution of 1:20 as cutoff, 10 of 14 (71%) ovarian carcinoma patients with NED and 9 of 21 (43%) patients with CED had antibodies to mesothelin compared with 6 of 23 (26%) healthy women (P < 0.008) and 5 of 24 (21%) women with other benign gynecologic diseases (P < 0.003), whereas 7 of 9 (78%) of women with pelvic inflammatory disease were positive. Three of the 14 (21%) NED patients had circulating mesothelin detected as an AU ≥ 0.2 at a serum dilution of 1:40 (P < 0.005) compared with 15 of 21 (71%) CED patients, and 9 of 14 (64%) NED patients (P < 0.0002) were positive for antibodies and negative for antigen compared with 1 of 21 (5%) CED patients. Although our data indicate that an antibody response to mesothelin is an important correlate of ovarian carcinoma, prospective studies are needed to show whether the measurement of such antibodies (alone or together with antigen) aids the diagnosis and monitoring of patients. (Cancer Epidemiol Biomarkers Prev 2008;17(6):1520–6)

Introduction

Mesothelin, a ~40-kDa protein that is expressed on cells from ovarian carcinoma, mesothelioma, and certain other tumors, is attracting increased attention both as a diagnostic marker (1-6) and as a therapeutic target (7). It is shed from tumor cells and can be detected in sera and other body fluids, primarily as mesothelin variant 1 (5). Mesothelin specifically binds to CA125 at the surface of ovarian carcinoma cells to mediate heterotypic cell adhesion, a finding suggesting that it may be involved in ovarian carcinoma pathogenesis and progression (8).

Many tumor antigens induce an immune response in cancer patients and healthy subjects (9). For example, antibodies to HER-2/neu and p53 have been detected by capture ELISA (10, 11) in patients with early-stage breast cancer. Anti-MUC1 antibodies have been reported to be more frequent in healthy women with characteristics associated with a decreased risk of developing ovarian carcinoma (12). In contrast, the demonstration of antibodies to certain other antigens that are expressed by both ovarian carcinoma and normal ovaries has led to the hypothesis that autoimmune disease of the ovary can be an early harbinger of potential ovarian carcinoma (13, 14).

Ho et al. reported that ~50% of patients whose tumors expressed mesothelin had antibodies that bound to recombinant mesothelin compared with 0% to 8% of patients whose tumors did not express mesothelin (15). To evaluate the potential clinical applications of measuring anti-mesothelin antibodies in patients with ovarian carcinoma, we have designed an ELISA to measure antibodies to native mesothelin and applied it to study sera from ovarian carcinoma patients who had no evidence of disease (NED) following therapy for advanced ovarian carcinoma as well as from patients with clinical evidence of disease (CED), and we also assayed the sera for mesothelin. For comparison, we studied sera from healthy women and from women with various benign gynecologic conditions, including pelvic inflammatory disease (PID).

Materials and Methods

Patients. We studied sera from 35 ovarian carcinoma patients selected from a larger group of such patients, all of whom diagnosed with and treated for ovarian carcinoma at the Gynecology-Oncology Department, Sheba Medical Center, from January 1, 2000 to January 31, 2003. All patients were routinely seen at the outpatient clinic of the Sheba Medical center, and sera were...
harvested over a 12-month period beginning February 1, 2003, with >75% of the patients providing at least three serial samples. The final evaluation of the patients’ health status was carried out in February 2005. The diagnosis of ovarian carcinoma was confirmed by histopathology in all patients. The clinical details were extracted from the medical records and, when needed, via a telephone interview with the patient. Patients were followed every 2 to 3 months for the first year after completion of first-line chemotherapy and every 3 to 4 months over the subsequent 2 to 4 years. All patients were treated with six to eight cycles of standard platinum and taxane-based regimens. For follow up, blood was withdrawn at the time of visit as part of a routine management scheme. The study was approved by the institutional review board, using criteria similar to those in the United States, and each patient signed a written consent form.

The status of the ovarian carcinoma patients was defined as NED (n = 14) or with CED (n = 21), 14 of which died of disease during the observation period. Sera were also harvested from 34 age-matched control women who had been inpatients or outpatients for diseases other than cancer, including 9 women who were diagnosed with PID, 14 women with endometriosis, and 7 women with ovarian cysts. In addition, sera were tested from an age-matched control group of 23 U.S. women who had no known diseases and specifically no gynecologic symptoms.

All 35 ovarian carcinoma patients were Jewish Israeli women, as were the 34 controls with benign gynecologic disease, except for 10 U.S. women with endometriosis who were patients at the University of Washington. Age at diagnosis was 56 ± 13 years (range, 28-84 years). Twenty-six of the cancer patients had serous ovarian carcinoma, 3 had adenocarcinoma, 4 had endometroid type carcinoma, and 2 had mucinous ovarian carcinoma. At the time of diagnosis, 2 patients were stage I, 1 patient was stage II, 30 were stage III, and 2 patients had metastatic stage IV disease.

**Serum Harvest.** Venous blood (10 mL) was withdrawn from each participant, and serum was separated using an established protocol (16).

**Assay for Circulating Mesothelin.** Although an assay, MESOMARK (17) was recently marketed, which measures mesothelin as quantitative protein units, it has not been evaluated for use in patients with ovarian carcinoma. We, therefore, applied an ELISA identical to that used by our group in several previous studies on sera from patients with ovarian carcinoma (1, 3, 5) or mesothelioma (2). In this assay, serum mesothelin levels are determined by a sandwich ELISA using two monoclonal antibodies (mAb; OV569 and 4H3), which bind to different mesothelin epitopes (1, 5). Serum samples are diluted 1:40 with PBS containing 3% bovine serum albumin (BSA). Mesothelin levels are determined as absorbance according to absorbance measurement by a microplate reader at A_{450} nm (1) and referred to as absorption units (AU). A serum is classified as positive for mesothelin when the AU at dilution 1:40 is ≥0.20 as in previous studies (1-3) and corresponds to 3 SD above the mean absorbance measurement at 450 nm as determined previously with a group of >100 healthy controls. Antigen was tested in the same sera as assayed for anti-mesothelin antibodies.

**Assay for Anti-Mesothelin Antibodies.** The first step toward constructing an assay for antibodies to native mesothelin was to isolate mesothelin from samples of urine of patients with metastatic carcinoma of the ovary or pancreas. mAb 569 (1) was dissolved in 0.1 mol/L NaHCO₃ buffer containing 0.5 mol/L NaCl (pH 8.5). Cyanogen bromide–activated Sepharose 4B (Sigma) was washed and swelled in cold 1 mmol/L HCl for 30 min and then washed with 10 volumes of water followed by 0.1 mol/L NaHCO₃/0.5 mol/L NaCl buffer. Immediately thereafter, mAb 569 was added to the washed resin at a concentration of 10 mg antibody/mL resin. Following 2-h incubation at room temperature, unbound antibody was removed by washing with NaHCO₃/NaCl buffer, and unreacted groups were blocked by incubation with 0.2 mol/L Tris-HCl (pH 8.0) overnight at 4°C. Urine samples were pretested by ELISA (1) to confirm the presence of a high level of mesothelin. The pH of the urine was adjusted by addition of 1 mol/L NaHCO₃ until it was >8.0, after which the sample was filtered. Sepharose 4B that had been conjugated with mAb 569 was washed with 10 volumes of PBS and the urine sample was added followed by washing with 10 volumes of PBS. Subsequently, mesothelin was eluted with 0.1 mol/L glycine-HCl (pH 2.7), after which the pH was neutralized by adding 2 mol/L Tris and the preparation was dialyzed against PBS.

As an alternative source, mesothelioma cell line Meso, which was established in our laboratory, was adapted to grow in Iscove’s modified Dulbecco’s medium without serum, and culture supernatant was collected every 5th day during 4 to 12 weeks of propagation of the cultured cells and frozen. After pooling culture supernatants and adjusting pH with NaHCO₃, the supernatants were filtered and run through a Sepharose 4B column conjugated with mAb 569. After washing the column with 10 volumes of PBS, mesothelin antigen was eluted from the column with glycine-HCl (pH 2.7).

ELISA (1) was done to confirm that the material isolated as described from either urine or culture supernatants was mesothelin, and sequencing studies were done to confirm that the purified material represented mesothelin as reported in Results.

The purified mesothelin was diluted in carbonate-bicarbonate buffer at 10 μg/mL and incubated overnight to coat the wells of a 96-well ELISA plate. After blocking for 2 h with 3% BSA, the plate was washed with PBS-0.1% Tween 20. Serum samples at dilutions 1:20 and 1:80 were added to each well and incubated at room temperature for 1 h, and 3% BSA was added in some wells as a negative control. After washing the plate with PBS-0.1% Tween 20, 1:1,000 diluted horseradish peroxidase–conjugated mouse anti-human IgG antibody (Invitrogen) was added to each well and incubated for 1 h at room temperature. After washing the plate with PBS-0.1% Tween 20, SureBlue TMB Microwell Peroxidase Substrate (KPL) was added to each well and incubated for 15 min at room temperature before the interaction was terminated by adding the TMB stop solution (KPL). AU was measured with a Dynatech MR5000 plate reader (Dynatech Laboratories). We evaluated the data at several cutoffs for the AU (0.2, 0.5, or 1.0) and at different dilutions of serum, but, except when otherwise stated, sera tested for antibodies were diluted 1:20 and AU ≥ 0.5 was used as cutoff for a
positive serum. One serum sample was tested from each healthy control subject and from each woman with a benign disease of the ovary (including PID). Sera from ovarian carcinoma patients were tested that had been harvested from three to five occasions when the clinical status was unchanged and the mean was calculated; the variation between the individual samples from the same patient was <10%. All tests were done on coded samples.

Antibody levels were measured in the same sera against mesothelin that had been purified from either urine or culture supernatants with the same source of antigen being used in each experiment with various sources of sera. There were no significant differences between the AU obtained when the same sera were tested against antigens from urine or supernatant (data not shown). We did not attempt to express the data as quantitative protein units but present them as AU, as done in related studies by others (12, 15), in view of difficulties to obtain appropriate standard curves, taking into account differences among polyclonal sera with respect to antibody avidities, mesothelin epitopes recognized, etc.

Characterization of Mesothelin in Urine and Culture Supernatants. Samples were purified by immunoaffinity chromatography using mAb 569 (1). Sequence analysis was done at the Harvard Microchemistry and Proteomics Analysis Facility by microcapillary reverse-phase high-performance liquid chromatography nano-electrospray tandem mass spectrometry on a Thermo LTQ-Orbitrap mass spectrometer. Tandem mass spectrometry spectra are then correlated with known sequences using the algorithm Sequest developed at the University of Washington (18) and programs developed by Chittum et al. (19). Tandem mass spectrometry peptide sequences were then reviewed for consensus with known proteins and the results were manually confirmed for fidelity.

Results

Characterization of Mesothelin Isolated from Urine or Culture Medium. Peptides recovered from liquid chromatography-mass spectrometry were examined for unique features to identify the different mesothelin isoforms. Variant 2 contains an 8–amino acid insertion as published previously (5). Variants 1 and 3 contain an Asp-to-Asn amino acid change and additional COOH-terminal sequence extensions, respectively. Both antigen sources were found to contain all three mesothelin variants based on the presence of the Asp-Asn replacement (data not shown). However, a lack of peptide resolution at the COOH-terminal end, which was also observed previously (5), remained a problem for detailed sequence analysis of variants 1 and 3. It should be noted that published sequence data may not be entirely reliable, and it is conceivable that the Asp-Asn replacement does not represent an actual protein peptide difference but rather an error in the initial sequence data retrieved from data banks and sequencing projects.

Pilot Experiments Titrating Sera from NED Patients and Healthy Controls. Experiments were done in which we titrated sera from ovarian carcinoma patients with NED following therapy as well as from healthy control women. One such experiment is presented in Fig. 1.

Whereas the serum from the healthy subject 8 gave no higher AU at any dilution than the negative control (BSA), the AU from patient 208 was higher than that of BSA also at dilution 1:640 and repeat tests of the same sera gave AU that varied with <10%. In other cases, sera from healthy controls were as reactive at dilution 1:20 as sera from patient 208 and gave as high titers (data not shown). To be conservative with the amount of available, purified antigen, we decided to do subsequent tests for antibodies (except when otherwise stated) with sera diluted 1:20 and use AU 0.5 as cutoff.

Antibody Assay Has Longitudinal Stability. We tested serial samples of 1:20 diluted sera from three ovarian carcinoma patients within a 4-month interval, during which there was no detectable change in the clinical state. One of these patients (patient 208) had NED and two patients (patients 305 and 310) had CED. AU with 1:20 diluted sera displayed very little variation (1.110, 1.079, and 1.062; 1.147, 1.259, and 1.103; and 0.148, 0.171, and 0.023, respectively).

Anti-Mesothelin Antibodies in Sera from Healthy Women and from Women with Nonneoplastic Diseases. We first tested sera (one sample per subject), diluted 1:20, from 23 healthy American women, none of whom had ever been diagnosed with cancer or any benign gynecologic disorder. The data are presented in Fig. 2A and summarized in Table 1. They show that 6 (26%) of these women had an AU > 0.5 and that 2 (9%) of them had an AU ≥ 1.0. The mean AU for serum diluted 1:20 was 0.474 ± 0.399 (Table 2). None of the healthy women had circulating mesothelin when tested at a dilution of 1:40 and using AU 0.2 as cutoff (data not shown).

As shown in Fig. 2B, 5 of 34 women with nonmalignant gynecologic conditions, but excluding PID, had sera with an AU ≥ 0.5 at dilution 1:20 for a mean reactivity of 0.305 ± 0.262 (Table 2). Three of the 5 women whose sera were positive with the criteria applied had ovarian cysts. Fourteen of the women, including 4 from Israel (171-174) and 10 from the United States (175-184) had endometriosis, and all of them were negative for antibodies.

Serum samples were also tested from 9 women with PID. At a dilution of 1:20, sera from 7 (78%) sera of these donors had an AU > 0.5, 3 (33%) had an AU ≥ 1.0 (Fig. 2), and mean AU was 0.785 ± 0.549 (Table 2). The difference in mean AU for sera from women with

Figure 1. Titration of sera from one ovarian carcinoma patient (#208, ●) with NED and one healthy control donor (#8, ■). BSA (▲) was tested as a negative control.
PID was different from that of sera from women with other benign gynecologic diseases ($P < 0.001$); the $P$ value in comparison with sera from healthy women was $<0.085$ (Table 2).

**Anti-Mesothelin Antibodies and Mesothelin in Sera from Ovarian Carcinoma Patients with NED.** Sera were tested for the presence of anti-mesothelin antibodies from 14 patients who had NED following therapy for stage III or IV ovarian carcinoma. As shown in Fig. 3A, 10 (71%) patients had an AU $>0.5$ and 6 (43%) had an AU $>1.0$ when tested at a dilution of 1:20. The difference in the percentage of positive patients with NED in comparison with healthy donors was significant, also at a dilution of 1:80 and when using two different cutoffs for the AU (Table 1). Likewise, the differences in mean AU were significant in comparison with sera from healthy women or women with benign diseases other than PID (Table 2).

As shown in Fig. 3B, 3 of 14 (21%) NED patients had sera that were positive for mesothelin when tested at a dilution of 1:80. One of them (209) had detectable anti-mesothelin antibodies, whereas the two others (213 and 215) did not.

**Anti-Mesothelin Antibodies and Mesothelin in Ovarian Carcinoma Patients Alive with CED.** Figure 4A and Table 1 show that 1:20 diluted sera from 9 of 21 (43%) patients with CED had antibodies detected at an AU $>0.5$ and sera from 3 (14%) patients had an AU $>1.0$. Table 1 further shows that, at a serum dilution of 1:80 and applying AU $>0.5$ or $>0.2$ as cutoff, 4 (19%) and 13 (62%) of the 21 CED patients were positive compared with 2 (9%) and 7 (30%) of 23 healthy women, respectively; the difference between 13 of 21 and 7 of 23 is significant at $P < 0.036$. Sera from 15 of the 21 (71%) patients with clinical evidence of ovarian carcinoma were positive for mesothelin using an AU $>0.2$ at dilution of 1:40 (Fig. 4B).

As can be deduced from Figs. 3 and 4, 3 of the 14 (21%) patients with NED and 15 of the 21 (71%) patients with CED had circulating mesothelin ($P < 0.005$), and 9 of the 14 (64%) patients in the NED group were antigen negative and antibody positive compared with 1 of 21 (5%) patients in the CED group ($P < 0.0002$). Two of 14 (14%) NED patients had circulating mesothelin and no detectable antibodies compared with 7 of 21 (33%) patients with CED. Eight of 21 (38%) patients with CED had both antibodies and circulating mesothelin compared with 1 of 14 (7%) patients in the NED group ($P < 0.04$).

**Discussion**

Most ovarian carcinoma express mesothelin (1, 7, 20, 21) as do mesotheliomas (2) and certain other tumors, including pancreatic adenocarcinomas. Antibodies to
mesothelin are more frequent in patients with ovarian carcinoma than in healthy controls (6), and T-cell immunity to mesothelin was shown in some patients with pancreatic carcinoma who had been immunized with genetically modified tumor cells and displayed a more favorable clinical outcome (22). An assay measuring mesothelin in serum has been reported to complement CA125 for the diagnosis of ovarian carcinoma (3) and aid the diagnosis of mesothelioma (2).

Using an assay to measure antibodies to native mesothelin, which was isolated from either urine or supernatants of a cultured mesothelioma, we now report that high antibody levels were more frequent in women who had NED after treatment for advanced ovarian carcinoma than in women with CED or in control groups, except for women who had been diagnosed with PID. In agreement with previous publications (2, 3), circulating mesothelin was more frequently detected in the CED group than in patients with NED (71% versus 21%) and more patients in the CED than in the NED group (38% versus 7%) had both circulating mesothelin and anti-mesothelin antibodies.

Anti-mesothelin antibodies may have several functions that can influence the clinical outcome and measuring such antibodies may provide information about a patient’s response to therapy. Such antibodies have been reported to inhibit the binding between mesothelin and CA125, which may decrease tumor invasiveness (8), and they may, like antibodies to many other antigens at the surface of tumor cells, mediate complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity (23). Furthermore, by forming immune complexes in the presence of antigen, they may facilitate the uptake of mesothelin by the Fc receptors on antigen-presenting cells, an event that may increase the generation and expansion of tumor-directed T cells, including T cells with suppressive activity (24). Anticancer therapy is likely to influence antibody formation both by decreasing the number of tumor cells releasing antigen and by killing or inhibiting antibody-forming cells.

Seven of the 9 women diagnosed with inflammatory pelvic disease (78%) had high antibody levels compared with a much lower percentage of women with other benign gynecologic diseases (15%) or healthy women (26%). However, these findings are hard to interpret without any direct evidence that the women diagnosed with PID had an immunologic event that involved the ovary. Antibodies have been implicated as promoters of tumor growth in some systems (e.g., in a mouse

Table 1. Relationship between clinical status anti-mesothelin antibodies in serum diluted 1:20 or 1:80 at two different AUs as cutoff

<table>
<thead>
<tr>
<th>Donor</th>
<th>Serum Dilution 1:20, AU ≥ 0.5, n (%)</th>
<th>Serum Dilution 1:80, AU ≥ 0.5, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy (23)</td>
<td>6 (26)</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Benign, except for PID (34)</td>
<td>5 (15)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Ovarian carcinoma, NED (14)</td>
<td>10 (71)*</td>
<td>6 (43)</td>
</tr>
<tr>
<td>Ovarian carcinoma, CED (21)</td>
<td>9 (43)</td>
<td>3 (14)</td>
</tr>
</tbody>
</table>

*P < 0.01, in comparison with serum from healthy women.
\( \dagger \)P < 0.005, in comparison with serum from women with benign disease, except for PID.
\( \ddagger \)P < 0.001, in comparison with serum from healthy women.
\( \times \)P < 0.05, in comparison with serum from patients with NED.

Table 2. Anti-mesothelin antibodies in sera diluted 1:20 measured as AU (mean ± SD) in the various groups

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Mean ± SD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Healthy</td>
<td>23</td>
<td>0.474 ± 0.399</td>
</tr>
<tr>
<td>2. Benign gynecologic disease (except for PID)</td>
<td>34</td>
<td>0.505 ± 0.262</td>
</tr>
<tr>
<td>3. PID</td>
<td>9</td>
<td>0.785 ± 0.549</td>
</tr>
<tr>
<td>4. Ovarian carcinoma, NED</td>
<td>14</td>
<td>1.11 ± 0.683</td>
</tr>
<tr>
<td>5. Ovarian carcinoma, CED</td>
<td>21</td>
<td>0.582 ± 0.397</td>
</tr>
</tbody>
</table>

*Statistical significance for the difference between groups 1 and 3 \( (P < 0.085) \), groups 2 and 3 \( (P < 0.001) \), groups 1 and 4 \( (P < 0.001) \), groups 1 and 5 \( (P < 0.37) \), and groups 4 and 5 \( (P < 0.008) \).

Figure 3. A. Data on anti-mesothelin antibodies in sera diluted 1:20 from 14 ovarian carcinoma patients who had NED. B. Mesothelin data from the same patients with sera diluted 1:40. Horizontal lines, cut off at AU 0.5 for antibodies and 0.2 for antigen.
melanoma model), where B cell–depleted mice did not develop tumor but only hyperplastic tissues unless they received either primed B cells or serum containing antitumor antibodies (25). It has been speculated that an immune response may be directly involved in facilitating malignant transformation or promotion of the malignant process (26). In spite of several provocative findings (13, 14, 27), further studies are needed to establish the relationship between autoimmune diseases of the ovary and ovarian carcinoma.

Our findings suggest that measurement of anti-mesothelin antibodies may complement measurements of mesothelin in women with ovarian carcinoma to aid in the monitoring of disease status and therapeutic response in patients with ovarian carcinoma. Because antibody levels have longitudinal stability, and because antibodies may also react to antigen released in too small an amount to be detected in serum, one should explore whether changes in antibody levels would predict tumor formation in high-risk groups. However, the results of this study should be interpreted with caution given the limitations of the study. The data emanate from a retrospective study based on a limited number of patients with ovarian carcinoma who were treated at a single medical center. Future, prospective, longitudinal, multicenter studies are needed to further evaluate whether changes in the level of anti-mesothelin antibodies, alone or in combination with assays for other biomarkers, will predict relapses and/or facilitate earlier diagnosis.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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Figure 4. A. Data on anti-mesothelin antibodies in sera diluted 1:20 from 21 ovarian carcinoma patients with CED. B. Mesothelin data from the same patients with sera diluted 1:40. Horizontal lines, cut off at AU 0.5 for antibodies and 0.2 for antigen.

References
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