Autoantibodies to Mesothelin in Infertility

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Abstract

Background: According to extensive epidemiologic data, infertility is associated with increased ovarian cancer risk. Previous studies showed that both women with infertility and those with ovarian cancer have autoantibodies to ovarian antigens. The objective was to determine if women with infertility have antibodies to mesothelin, a well-characterized ovarian cancer antigen.

Methods: Sera were obtained from women with infertility (n = 109), ovarian cancer (n = 28), benign ovarian tumors or cysts (n = 24), and from healthy women (n = 152). Infertility included those with a risk for ovarian cancer; endometriosis (n = 23), ovulatory dysfunction (n = 17), premature ovarian failure (POF; n = 25) and unexplained infertility (n = 44). Sera were assayed for mesothelin antibodies and for circulating mesothelin antigen by immunoassay and compared with assay control sera (n = 16) to determine a positive result.

Results: Mesothelin antibodies were significantly more frequent in women with prematurely reduced ovarian function including ovulatory dysfunction (59%), ovarian failure (44%) and unexplained infertility (25%) compared with controls. In contrast, women with endometriosis, who also have a high risk for ovarian cancer, did not have mesothelin antibodies. Serum levels of mesothelin were rarely elevated in women with infertility but were high in most patients with ovarian cancer.

Conclusions and Impact: We show for the first time that antibodies to mesothelin, a well-characterized ovarian cancer antigen, occur in some women with epidemiologic risk for ovarian cancer. The results suggest it may be possible to identify which women with infertility have ovarian cancer risk. Cancer Epidemiol Biomarkers Prev; 20(00); 1–9. ©2011 AACR.

Introduction

Numerous epidemiologic studies indicate that there is an association between infertility and ovarian cancer (1–5), independent of infertility drug treatment. In a recent study of infertility using a cancer registry in Sweden, the OR for ovarian cancer was 3.93 (6). According to a 25-year longitudinal investigation of more than 12,000 women in the United States, the standardized incidence ratio (SIR) for ovarian cancer risk in infertile women is double that of the general population (SIR = 1.98; refs. 7, 8).

Infertility affects more than 11% of reproductive age women and is defined as the failure to conceive during 1 year of unprotected intercourse (9, 10). Diagnostic categories of female infertility may involve endometriosis (uterine cells outside the uterus), tubal factors (inflamed or mechanically blocked fallopian tubes), uterine factors (e.g., failed implantation), and ovarian factors such as ovulatory dysfunction, diminished ovarian reserve (reduced or absent oocyte content which includes premature ovarian failure), unexplained infertility and multiple causes (9–11). Unexplained infertility is a diagnosis of exclusion used when the standard clinical and laboratory data are normal. Premature ovarian failure (POF) is defined as spontaneous menopause before age 40 (12–14) and may be induced or idiopathic.

Different categories of infertility have different ovarian cancer risk. In the longitudinal infertility study, the highest risk factors for ovarian cancer compared with the general population were nulliparity (never conceived; SIR = 1.98) and endometriosis (SIR = 2.48) followed by anovulation (SIR = 1.94; refs. 7, 8). Some factors are additive; for example, the SIR for women with endometriosis who never conceived was 4.19. A relationship between POF and ovarian cancer has not been examined systematically although there is evidence that early age at menopause (15–17) or follicle depletion and early ovarian failure (18, 19) is associated with ovarian cancer risk. In cross-sectional studies, unexplained infertility is associated with an increased risk for ovarian cancer [e.g., SIR = 2.94 (20) or OR = 1.19 (4)].
The etiologies for infertility are multifactorial and include genetic, environmental, endocrine, and autoimmune factors. We showed that some patients with unexplained infertility or POF (21–23) have antiovary antibodies that indicate an autoimmune disorder targeting the ovary (22, 24–26). In addition, a subset of women from all categories undergoing treatment for infertility have poor ovarian estrogen responses to follicle stimulating hormone (FSH); this is also associated with antiovary antibodies (27). Although FSH levels are the gold standard for assessing ovarian function (28), antiovary antibodies seem to be independently associated with subclinical changes in ovarian function (29).

Cancer patients often make antibodies to antigens that are expressed in tumor cells even though some of the antigens are also expressed by normal cells (30–35). Women with ovarian cancer also have antiovary antibodies similar to women with infertility (36) indicating they have a similar autoimmune response (30, 36, 37). This is congruent with reports of antitumor antibodies to a variety of antigens in ovarian cancer (30, 37, 38). It has been hypothesized that autoimmunity increases the risk for cancer (32, 35, 39, 40) and that a weak tumor-directed immune response can stimulate tumor growth (41, 42).

To gain more insight into the relationship among autoantibodies, infertility, and ovarian cancer, we tested sera from women with infertility for mesothelin antibodies. Mesothelin expression is elevated in ovarian tumors (43), is shed into the circulation (44) and circulating mesothelin has relatively high specificity for ovarian cancer (45, 46). Previous studies showed that mesothelin antibodies occur in women with ovarian cancer (47, 48) and pelvic inflammatory disease (48). Thus, mesothelin was chosen because it is one of the best characterized ovarian cancer antigens and has relatively high specificity for malignant cells (43).

### Materials and Methods

#### Patients

A total of 329 sera were assessed from healthy controls, infertility patients and cancer patients. All sera were collected according to protocols approved by the relevant Institutional Review Boards.

Infertility patient sera (n = 109) were collected from infertility clinics at Rush University Medical Center (n = 26), the Center for Human Reproduction (courtesy of Dr. Carolyn Coulam; n = 16) and the University of Ulm (courtesy of Dr. Cosima Brucker; n = 67). Sera represented idiopathic POF (n = 25), endometriosis (n = 23), ovulatory dysfunction (n = 17), and unexplained infertility (n = 44). The evaluation included semen analysis, a postcoital test, ovulation (luteal phase progesterone), tubal patency (open and unobstructed fallopian tubes), and measurement of FSH and estrogen. The average duration of infertility was 3.6 ± 1.5 (range 2–8) years for all study patients. The average number of prior in vitro fertilization treatment cycles was minimal (less than 1 per patient).

Patients with idiopathic POF experienced menopause at an average of age of 26.6 ± 9.1 years and had elevated, menopausal day 3 FSH levels (i.e., >10 mIU/mL; Table 1). Endometriosis patients were obtained from the infertility clinic (n = 14) or from the gynecology clinic (n = 9) and had surgically confirmed endometriosis without other conditions. Hormone levels were not available for the later group. For endometriosis patients obtained through the infertility clinic, day 3 FSH was in the normal range (Table 1). Ovulatory dysfunction was defined as oligomenorrhea (35–90 days between cycles) or anovulation (no evidence of ovulation) and excluded polycystic ovary syndrome (49). Women with ovulatory dysfunction had slightly elevated, but near normal, day 3 FSH levels.

#### Table 1. Summary of patient characteristics

<table>
<thead>
<tr>
<th>Patient category</th>
<th>n</th>
<th>Age mean ± SD (range), y</th>
<th>FSH mean ± SD (range), mIU/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>31</td>
<td>38.7 ± 15.9 (18–65)</td>
<td>nd</td>
</tr>
<tr>
<td>Group II</td>
<td>121</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Infertility patients</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Endometriosis (infertility clinic)</td>
<td>14</td>
<td>38.3 ± 7.7 (28–60)</td>
<td>7.1 ± 2.6 (4.9–12.1)</td>
</tr>
<tr>
<td>Endometriosis (gynecology clinic)</td>
<td>9</td>
<td>46.0 ± 11.1 (36–70)</td>
<td>nd</td>
</tr>
<tr>
<td>Ovulatory dysfunction</td>
<td>17</td>
<td>31.7 ± 4.7 (24–40)</td>
<td>16.9 ± 24.9 (1.2–72)</td>
</tr>
<tr>
<td>POF</td>
<td>25</td>
<td>30.1 ± 6.6 (19–42)</td>
<td>60.4 ± 37.8 (19.1–123)</td>
</tr>
<tr>
<td>Unexplained infertility</td>
<td>44</td>
<td>33.2 ± 4.7 (21–49)</td>
<td>7.4 ± 3.1 (1.9–16.5)</td>
</tr>
<tr>
<td>Benign tumor or cyst</td>
<td>24</td>
<td>56.5 ± 15.7 (26–85)</td>
<td>nd</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>28</td>
<td>56.5 ± 15.7 (26–85)</td>
<td>nd</td>
</tr>
<tr>
<td>Assay serum controls</td>
<td>16</td>
<td>56.5 ± 15.7 (26–85)</td>
<td>nd</td>
</tr>
<tr>
<td>Total</td>
<td>329</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

nd = not determined.
Autoantibodies to Mesothelin in Infertility

Plasmid DNA was extracted with a MiniPrep kit (Qiagen) and then examined for inserts of the expected sizes by enzyme digestion (XhoI and SbfI), PCR, and sequencing.

Endotoxin-free mesothelin recombinant plasmid was prepared with an Endo-free Maxi kit (Qiagen). Two microgram plasmid was added into 2 μL of Lipofactamine and incubated (20 minutes). DNA-Lipofactamine complexes were added into 1 million CHO-DG44 cells. The cells were grown in suspension in 125 mL Corning plastic cell culture flasks and incubated (37°C; 5% CO₂, 95% air; 24 hours). The cells were transferred into selection medium (CHO medium without HT supplement). The number of transfected cells was greater than 95% after 30 days.

Culture media were tested for mesothelin using a sandwich ELISA (51, 52). Supernatants were diluted in PBS containing 1% BSA in a ratio of 1:10. The data showed that mesothelin was highly expressed by the CHO cells and was released into the culture media. Mesothelin was purified from the culture supernatants by an antibody affinity chromatography column and the purified mesothelin was verified by protein sequencing.

**Antibody tests**

Sera were tested at a dilution of 1:20 for antibodies to recombinant human mesothelin and selected sera were restested at a dilution of 1:100 using a modified assay (48). Briefly, plates (Medisorp; Fisher Scientific) were coated (100 uL/well, 16 hours, 4°C) with recombinant mesothelin in PBS (10 mmol/L, pH 7.4). For each serum, control wells without antigen (coating buffer only) were similarly incubated as a control for nonspecific binding of serum to plastic. Nonspecific binding was blocked with 3% BSA in PBS (450 nm with a Dynatech MR5000 plate reader (Dynatech Laboratories). For each serum sample, optical density values in wells without antigen were subtracted from the optical density value in wells with mesothelin. Data was analyzed either by comparison of optical density values or using a cutoff value to determine an antibody positive result. The cutoff value was equivalent to the mean optical value for the serum assay controls (n = 16) plus 2 SD (95% CI) or 3 SD (99% CI).

**Measurement of circulating mesothelin**

Mesothelin levels in sera were measured using a standard sandwich immunoassay (R&D Systems). Rat anti-human mesothelin capture antibody and biotinylated rat anti-human mesothelin detection antibody were used according to the manufacturer’s instructions. Mesothelin was measured in sera diluted 1:40 in Reagent Diluent...
The recombinant human mesothelin standard curve range was 62.5 to 8,000 pg/mL. The analytic limit of detection (negative control mean + 2SD) was 79.3 pg/mL.

**Statistical analysis**

The Mann–Whitney U test was used to compare the optical density values and the mesothelin levels. Significant differences in the proportion of mesothelin antibody positive sera were determined using the Fisher's exact test. The correlation between mesothelin levels and anti-mesothelin optical density values was compared and significance was determined using Pearson's or Spearman's rank correlation as appropriate. For all tests \( P < 0.05 \) was considered significant.

**Results**

In an initial analysis of mesothelin antibody levels the 2 comparison groups (normal-I and normal-II) were evaluated separately and in combination. Since there was no difference between normal-I and normal-II (\( P > 0.6 \)) using either the optical density values or a cutoff value to determine the number of antibody positive sera, and since results were similar when the groups were combined, all further analysis used the combined normal sera group for comparisons.

The mean levels of antibody measured as the optical density at 1:20, were significantly higher in women with POF \( (P = 0.00001) \), ovulatory dysfunction \( (P = 0.0003) \), unexplained infertility \( (P = 0.038) \), and endometriosis \( (P = 0.041) \) compared with normal sera (Fig. 1 and Table 2). Optical density values for sera from women with ovarian cancer or benign tumors did not differ and they did not differ from normal sera \( (P > 0.2) \).

When a cutoff value (95% CI) was used (Table 2), the number of positive sera was significantly higher in

| Table 2. Summary of mesothelin antibody and antigen in infertility |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | OD value        | Antibody        | Antibody        | Antigen level   |
|                 | Mean ± SD       | % POS (2SD) (%/total) | % POS (3SD) (%/total) | Mean ± SD (ng/mL) | Mean ± SD (range) |
| Normal          | 0.37 ± 0.4      | 19% (29/152)    | 11% (17/152)    | 0.16 ± 0.10     | 6% (5/82)        | 18.6 ± 8.5 (10.2–49.6) |
| Inertility patients |                |                 |                 |                 |
| Endometriosis   | 0.47 ± 0.34*   | 35% (8/23)      | 26% (4/23)      | 0.19 ± 0.14     | 14% (3/22)      | 16.9 ± 7.7 (8.3–37.8) |
| Ovulatory dysfunction | 1.01 ± 0.74*** | 65% (11/17)** | 59% (10/17)** | 0.49 ± 0.38*** | 50% (8/16)** | 24.1 ± 8.4 (11.7–33.3) |
| POF             | 0.88 ± 0.78*** | 52% (13/25)**  | 44% (11/25)**  | 0.53 ± 0.51*** | 33% (5/15)**  | 20.5 ± 9.9 (10.8–45.6) |
| Unexplained infertility | 0.53 ± 0.51* | 32% (14/44)    | 25% (11/44)*   | 0.24 ± 0.21     | 26% (10/38)** | 24.7 ± 12.3 (12.6–59.1) |
| Benign tumor or cyst | 0.38 ± 0.35  | 21% (5/24)     | 21% (5/24)     | 0.16 ± 0.11     | 0 (0/18)      | 14.1 ± 6.9 (6.0–32.5)  |
| Ovarian cancer  | 0.41 ± 0.33    | 36% (10/28)     | 14% (4/28)     | 0.15 ± 0.13     | 11% (2/18)     | 102.9 ± 113.9 (12.1–434.7)** |
| Assay serum control | 0.27 ± 0.13 | ref.           | ref.           | 0.19 ± 0.09     | ref.          | 12.0 ± 5.6 (5.3–38.1)  |

Significance is indicated as *, \( P = 0.05–0.01; **, P = 0.01–0.001; ***. P < 0.001.\)
women with POF ($P = 0.002$) and ovulatory dysfunction ($P = 0.0002$) compared with normal sera. The number of positive sera in unexplained infertility, endometriosis or benign conditions did not differ from normal sera ($P > 0.2$). The number of positive sera in ovarian cancer ($P = 0.077$) and unexplained infertility approached significance ($P = 0.097$) compared with normal sera. Within the ovarian cancer group, mesothelin antibody occurred in 50% (8 of 16) sera from women with serous histology tumors, only 11% (1 of 9) sera from patients with endometrioid tumors and 1 serum from a patient with mixed clear cell and endometrioid tumor.

Two more stringent conditions for determining the number of positive sera were used. A higher cutoff value (99% CI) reduced the proportion of positive sera in all groups (Table 2). Using the higher cutoff value, sera from women with POF ($P = 0.0005$) or ovulatory dysfunction ($P = 0.0001$) remained significantly different from normal sera.

Similarly, when sera were tested at a higher dilution of 1:100, only the optical density values for POF ($P = 0.0001$) and ovulatory dysfunction ($P = 0.00008$) differed significantly compared with normal sera (Table 2). However, the number of positive sera (95% CI) in unexplained infertility ($P = 0.005$) became significant and the number of antibody positive sera remained significant in POF ($P = 0.007$) and ovulatory dysfunction ($P = 0.0001$).

Overall, the decrease in the proportion of positive sera associated with dilution of sera from 1:20 to 1:100 was greater than 75% for benign conditions, endometriosis, normal, and ovarian cancer, while the relative decrease of antibody positive sera in infertility groups was less than 40%. Taken together the results show that mesothelin antibodies in the infertility groups, particularly POF and ovulatory dysfunction, have a higher titer and possibly a higher affinity than antimesothelin detected in normal, benign or ovarian cancer sera.

Mesothelin antigen levels in serum were significantly higher in women with ovarian cancer ($P = 0.00003$), benign conditions ($P = 0.01$) or unexplained infertility ($P = 0.01$) compared with normal women (Fig. 2 and Table 2). On the basis of optical density values, mesothelin antibody and antigen were not correlated (Spearman’s correlation coefficient, 0.06, $P = 0.4$). Within individual categories, mesothelin antigen, and antibody were not significantly correlated except in ovarian cancer (correlation coefficient $= 0.49$, $P = 0.015$). However, as seen in Figure 3, the association is scattered; some individuals have elevated mesothelin, some have mesothelin antibody, and some have both.

Although the age range of the study groups and normal controls overlapped, the mean ages were not the same. Mesothelin antibody (correlation coefficient $= −0.17$, $P = 0.02$) was negatively correlated, while mesothelin antigen (correlation coefficient $= 0.26$, $P = 0.001$) was positively correlated with age. When corrected for age, the relationships between antimesothelin and circulating mesothelin remained unchanged (correlation coefficient $= 0.1$, $P = 0.2$) including the correlation within the ovarian cancer group (correlation coefficient corrected for age $= 0.49$, $P = 0.018$). Thus, circulating antigen was detected more often in ovarian cancer and antimesothelin was detected more often in patients with evidence of ovarian failure.

Discussion

This study extends previous studies which showed that women with infertility and women with ovarian...
cancer have antibodies to ovarian antigens and shows for the first time that women with specific categories of infertility have antibodies to a well-known ovarian cancer biomarker. Originally, we identified antiovarian (micronomal) antibodies indicative of ovarian autoimmunity in women with POF, unexplained infertility or suboptimal response to exogenous hormone (21–27, 29, 53–55). Furthermore, in women with low ovarian responsiveness, antiovarian antibodies occur predominantly in younger women differentiating them from older women transitioning into a normal, age-related menopause (53). Since women with infertility have increased risk for ovarian cancer (4, 6, 8) and since antitumor antibodies are common in cancer (30, 35, 38, 56–58), we also evaluated the possibility that ovarian cancer patients have antiovarian antibodies. We found that women with ovarian cancer, but not endometrial cancer or benign tumors have antiovarian antibodies (36).

In the current study, we show that there is an autoantibody response to mesothelin, a well-defined biomarker of ovarian carcinoma (51, 59, 60), in women with POF, ovulatory dysfunction or unexplained infertility. This is consistent with the presence of an autoimmune disease of the ovary (22, 24–26, 61) and with the established risk of ovarian cancer associated with infertility (4, 6, 8). This raises the possibility that an autoimmune process precedes or contributes to development and progression of malignant ovarian tumors. Shared autoantibody repertoires in autoimmunity and cancer have been reported (32). Although there is a relationship between autoimmunity and immunity to tumors, the nature of the relationship remains to be determined (39). Nonetheless, the results of this study suggest that early autoantibody responses could identify which women with infertility have a high risk for ovarian cancer.

Interestingly, although endometriosis is associated with a high risk for ovarian cancer (62, 63), women with endometriosis did not have antimesothelin antibodies. Although there was a difference in the initial, least stringent analysis of optical density values, there was no difference in the number of positive sera compared with normal sera. The absence of mesothelin antibodies in patients with endometriosis was also noted in a small group in a previous study (48). A history of endometriosis is more often associated with endometrioid and clear cell ovarian carcinoma (62) while serous histology tumors are thought to arise from epithelial cells shed onto the ovary from the fallopian tubes (64, 65). Similarly, the risk for subtypes of ovarian tumors may vary; among women with infertility in a population study of infertility in Denmark (66), the major contribution to ovarian cancer risk was associated with serous tumors (SIR = 2.1) followed by endometrioid tumors (SIR = 1.35) with mucinous tumors contributing little to the risk for ovarian cancer (SIR = 0.81). This is also consistent with differences in expression profiles among different tumor subtypes (67, 68). Thus, it is possible that tumors arising in women with endometriosis do not involve autoantibody reactions or do not involve the same autoantibody reactions as other infertility categories.

Evidence for different autoantibodies associated with different histologic subtypes (30, 69–71) is congruent with the concept that mesothelin antibodies may be associated with some types of infertility and not others. We found the majority of mesothelin antibody positive sera in ovarian cancer were associated with serous rather than endometrioid tumor histology, consistent with the more frequent expression of mesothelin in serous ovarian tumors (72). Hence it is possible that antibodies to mesothelin reflect a risk for serous ovarian tumors.

In addition, we found a higher titer of antimesothelin antibodies in infertility than in ovarian cancer. This suggests they may have a higher affinity, or that in ovarian cancer in the presence of excess antigen, antibody-antigen complexes form reducing detection of antimesothelin. Antigen-antibody complexes have been reported for CA125 (73) and MUC1 (74). It is also possible that excess antigen or some other mechanism suppresses the antibody response in ovarian cancer. Although mesothelin antibodies were reported previously (47, 48) our group of ovarian carcinoma patients may have been too small to reach statistical significance compared with normal sera. However, the group used in this study had a lower proportion of serous ovarian cancer than in prior studies (47, 48) and this may have contributed to the lower proportion of mesothelin antibodies. Although none of the normal or benign comparison groups had significant levels of antimesothelin, there were occasional women with mesothelin antibodies. This is not surprising since more than 11% of the population may have infertility (9) and thus it is possible that a subset of women in the normal group may have infertility associated with autoantibodies. It is also possible that among older women in this group a subset have undetected early stage tumors. Thus, the magnitude of differences between women with identified infertility and those in the normal group may be slightly underestimated. However, further study is needed to determine the significance of mesothelin antibodies in apparently healthy women.

We also tested sera for circulating mesothelin and found, as expected, that most patients with ovarian carcinoma had circulating antigen (45). However, with the exception of unexplained infertility, circulating antigen was not significantly higher in the infertility groups compared with normal women. Since there are no standard clinical cutoff values for circulating mesothelin, it is not clear if the slightly elevated levels of circulating mesothelin in unexplained infertility are clinically relevant.

The precise function of antibodies in tumor progression remains to be determined and may involve multiple roles (75). Antibodies to cell surface antigens can promote the growth of tumor cells both in vitro and in vivo (76–78). Antibodies to tumor antigens can also inhibit tumor growth, for example, via antibody-dependent cellular cytotoxicity, complement dependent cytotoxicity and
by interfering with growth controlling signals. Also, a weak tumor-directed immune response can stimulate tumor growth (41, 42) and it has been hypothesized that autoimmunity increases the risk for cancer (32, 35, 39, 40). However, in contrast to the extensive evidence for anti-tumor antibodies, MUC1 antibodies, another antigen which is overexpressed in ovarian cancer (79–81) are detected more frequently in women with a lower risk of ovarian cancer (80, 81) than in patients with cancer (82, 83). Clearly, antitumor antibodies may provide specific biomarkers of cancer risk and of early stage cancer, but much remains to be determined regarding their functional role in cancer.

In summary, the results of this study showed for the first time that circulating mesothelin antibodies occur in women with increased epidemiologic risk for ovarian cancer. One may speculate that antibodies may arise in response to very early neoplastic processes in infertile women that may or may not progress to malignant tumors depending on additional triggering events. On the other hand antibodies may bind to normal cells in the ovary and cause ovarian dysfunction which leads to infertility and in a subpopulation of infertile women, to the development of ovarian cancer. On the other hand, antibodies may simply reflect an inflammatory response to mesothelin.

Further studies are needed to establish the relative risk for ovarian cancer in infertile women who have mesothelin antibody. Useful information on the relationship of autoantibodies to tumor progression may also be derived from an appropriate animal model. For example, we showed that egg-laying hens have a high frequency of ovarian carcinoma (84) associated with ovarian autoantibodies similar to humans (85). Ovarian tumors in hens express a homologue of human mesothelin (86). Use of this model may facilitate clarification of the relationship between antimesothelin antibodies and ovarian cancer formation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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