Detection of Mammary Serum Antigen in Sera from Breast Cancer Patients Using Monoclonal Antibody 3E1.2

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ABSTRACT

Murine monoclonal antibody 3E1.2, made against human breast cancer cells, detects a glycoprotein (Mr > 300,000) called mammary serum antigen (MSA) which is elevated in the serum of patients with breast cancer. An enzyme immunoassay was developed to detect MSA in human serum and used to detect MSA in subjects with breast cancer and other diseases. Raised levels of MSA (>300 inhibition units) were found in the serum of 1.9% of 2406 blood donors, in 18% of sera from 40 subjects with benign breast disease, and in 16% of sera from 222 subjects with non-breast cancers. However, in patients with a diagnosis of breast cancer, 76% (84 of 110) of Stage I and II, and 86% (142 of 166) of Stage III and IV had levels of >300 inhibition units. Nineteen percent of patients, classified clinically disease free, had raised MSA levels. In 34 of 37 (92%) patients followed over 2 to 11 mo the level of MSA correlated with the clinical course of disease. Changes in MSA levels not only corresponded to changes in the clinical course of disease, but also preceded the clinical detection of progressive disease. Immunoblotting has detected a heterogeneous molecule of Mr > 300,000 and been used to confirm the elevation of MSA in breast cancer patients. Determination of MSA level may be useful for the detection of breast cancer and for monitoring progress of disease and response to therapy.

INTRODUCTION

In the Western world, breast cancer accounts for more deaths in women than any other malignancy. One in 14 women will develop breast cancer during their lifetime; however, the disease is potentially curable if diagnosed at an early stage, and early detection is associated with a better prognosis. The detection of low bulk minimal metastatic disease may also be associated with improved prognosis. It is therefore important to develop new methods for the early diagnosis of breast cancer, for monitoring patients with known disease, and for the early detection of the recurrence of disease.

In theory, assaying levels of tumor antigens in serum, which accurately reflect the tumor burden, is a simple, noninvasive means of diagnosing and monitoring patients with breast cancer. The advent of hybridoma technology has led to the description of a number of monoclonal antibodies defining breast cancer-associated antigens in serum. More recently, immunoassays quantitating these breast cancer-associated antigens in serum have been described. In general, they possess improved sensitivity and specificity over markers previously described. However, none of these assays which have previously been described can be used to monitor all patients with breast cancer or for screening asymptomatic individuals. Clearly there is a need for more specific and sensitive serum assays for breast cancer, or at least those which can complement preexisting tests and enable the detection of increased numbers of patients.

We have developed a serum test for the detection of breast cancer based on the use of a monoclonal antibody 3E1.2. This antibody was developed against fresh primary human breast cancer cells and reacts with >90% of breast tumors by the immunoperoxidase technique, but has a limited reactivity with other normal tissues, and no reactivity with human milk fat globule membranes. Binding studies have shown that MSA is related to other high-molecular-weight glycoproteins, previously defined in human milk and breast cancer. However, monoclonal antibody 3E1.2 lacks reactivity with all components of human milk and therefore defines a unique epitope, previously undetected.

The 3E1.2 antibody has also been found to be useful for the detection of breast cancer in tissue sections and for the localization of breast cancer in axillary lymph nodes by immunoscintigraphy using radiiodinated 131I-3E1.2. 3E1.2 also detects an antigen in serum (MSA), the level of which is raised in patients with breast cancer. This antigen is present on a high-molecular-weight glycoprotein (Mr > 300,000), which has been isolated and characterized from human serum. The purpose of this study was to determine the serum levels of MSA in the normal population, patients with breast cancer, benign breast disease, and other cancers and to assess the usefulness of these levels for detecting localized breast cancer and monitoring the disease.

MATERIALS AND METHODS

Serum Samples. Normal serum samples (2406) were obtained from apparently healthy blood donors at Red Cross blood banks (Melbourne, Victoria, Australia, and Newcastle, New South Wales, Australia). These consisted of 1300 females and 1000 males aged between 18 and 65 yr (sex not recorded in 106 donors). Serum samples from patients with breast cancer and other diseases were also obtained (see Tables 1 and 2 for details, see acknowledgements for sources). The criteria for staging and disease status are in accord with accepted definitions. Serum samples were also obtained at regular intervals (over 2 to 11 mo) from 37 patients undergoing treatment and observation for breast cancer. Serum samples were collected at the time of each clinical assessment and were retrospectively selected to correlate with the onset of first clinical change. Serum samples were obtained from clotted blood, aliquoted, and stored at −70°C until use.

Competitive Enzyme Immunoassay. MSA used in the competitive enzyme immunoassay was extracted from a breast cancer cell line or from fresh carcinoma by homogenization in 0.25 M sucrose:25 mM Tris:1 mM EDTA, pH 7.4. Serum samples were then incubated with an antibody raised against human milk and breast cancer. The 3E1.2 antibody was then added to the competitive enzyme immunoassay and the reaction was stopped with addition of substrate. The absorbance was measured at 450 nm and the results were expressed as percent inhibition of reaction. The absorbance of the control reaction was defined as 100% inhibition. The results were expressed as percent inhibition of reaction. The absorbance of the control reaction was defined as 100% inhibition. The results were expressed as percent inhibition of reaction.

The abbreviations used are: MSA, mammary serum antigen; PBS, phosphate-buffered saline; BSA, bovine serum albumin; SDS, sodium dodecyl sulfate; PAGE, polyacrylamide gel electrophoresis. 1 Recipient of a Commonwealth Postgraduate Research Award. 2 To whom requests for reprints should be addressed.
Table 1  MSA levels in patients with breast cancer, benign breast disease, and normal individuals

<table>
<thead>
<tr>
<th>MSA levels group</th>
<th>No. tested</th>
<th>Mean ± SE</th>
<th>% above 300 inhibition units</th>
<th>P (relative to normal females)</th>
<th>P (relative to benign breast disease)</th>
<th>P (relative to breast cancer Stage I)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal individuals</td>
<td>2406</td>
<td>125 ± 1.8</td>
<td>1.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease present*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>60</td>
<td>679 ± 86</td>
<td>72</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>50</td>
<td>946 ± 206</td>
<td>82</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>24</td>
<td>1184 ± 315</td>
<td>75</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>142</td>
<td>3861 ± 322</td>
<td>87</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Stage III and IV</td>
<td>166</td>
<td>3471 ± 324</td>
<td>86</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>No evidence of disease*</td>
<td>13</td>
<td>356 ± 268</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>51</td>
<td>192 ± 36</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>8</td>
<td>184 ± 35</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not staged</td>
<td>6</td>
<td>140 ± 67</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In remission Stage IV</td>
<td>31</td>
<td>681 ± 278</td>
<td>26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign breast disease/</td>
<td>40</td>
<td>157 ± 26</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Patients with clinically detected, active breast cancer.
* P < 0.05 considered significant.
* NS, not significant.
* Include bone metastases (n = 38), liver metastases (n = 11), lung and pleural metastases (n = 20), multiple metastases (n = 73).
* Patient previously having breast cancer but now with no clinically detected disease.
* Patients with histologically proven benign breast disease; this includes fibroadenoma, lobular hyperplasia, cystic hyperplasia, and gynecomastia.

Table 2  MSA levels in patients with non-breast cancer

All cancers were at an advanced stage when the serum samples were obtained.

<table>
<thead>
<tr>
<th>MSA levels group</th>
<th>No. tested</th>
<th>Mean ± SE</th>
<th>% above 300 inhibition units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung carcinoma</td>
<td>12</td>
<td>373 ± 235</td>
<td>8</td>
</tr>
<tr>
<td>Colorectal carcinoma</td>
<td>26</td>
<td>719 ± 383</td>
<td>19</td>
</tr>
<tr>
<td>Pancreatic carcinoma</td>
<td>103</td>
<td>371 ± 208</td>
<td>18</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>28</td>
<td>152 ± 33</td>
<td>18</td>
</tr>
<tr>
<td>Adenocarcinoma of an unknown primary</td>
<td>9</td>
<td>1323 ± 33</td>
<td>22</td>
</tr>
<tr>
<td>Genitoourinary*</td>
<td>12</td>
<td>105 ± 13</td>
<td>0</td>
</tr>
<tr>
<td>Embryonic*</td>
<td>7</td>
<td>170 ± 105</td>
<td>14</td>
</tr>
<tr>
<td>Miscellaneous*</td>
<td>16</td>
<td>289 ± 211</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>213</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>

* Includes carcinoma of the ovary, cervix, uterus, testis, and bladder.
* Includes teratomas and tumors of germ cell origin.
* Includes thymoma, melanomas, myelomas, sarcomas, and carcinomas of the stomach and prostate.

RESULTS

Immunoblotting of Patients' Sera

The relative molecular weight (M_r) of the molecules which carry antigenic determinants for the monoclonal antibody...
3E1.2 was determined by immunoblotting of sera separated by SDS-polyacrylamide gel electrophoresis. Fig. 1 shows the reactivity of monoclonal antibody 3E1.2 on sera pooled from normal subjects and patients with breast cancer. Heterogenous Mr > 300,000 bands were observed for both patients with advanced and local breast cancer, as well as the normal subjects (the heterogenous pattern in normal individuals required over-developing of the blots, data not shown). There was, however, a clear difference in intensity of the bands; more intense bands were seen in patients with breast cancer [e.g., Fig. 1, lanes 2 and 4, CaB St I (High)] compared to normal individuals (e.g., Fig. 1, lane 1, NHS). Also, the level of expression broadly correlated with inhibition unit values determined by the competitive enzyme immunoassay. The immunoblotting, although less sensitive than the competitive enzyme immunoassay, demonstrates that increased levels of serum MSA are present in patients with breast cancer.

MSA Levels in Serum Samples

Normal Individuals. A distribution of MSA levels seen in normal blood donors is shown in Fig. 2. In general low levels of MSA were found in the serum of apparently healthy blood donors; however, using an arbitrary cut-off level of 300 inhibition units, 1/9% of the 2406 normal individuals had raised MSA levels (Table 1). The mean level (±SD) of MSA in males was 116 ± 90 inhibition units, and was slightly, but significantly, higher in females 130 ± 88 inhibition units ($P < 0.001$). Of the 1/9% of normal subjects with raised levels [number examined (n) = 46], 17 subjects had high levels of MSA ranging from 799 to 5283 inhibition units. A proportion (10/17) of these individuals were subject to clinical examination and mammography for overt evidence of breast cancer or other diseases.

No disease was detected in any of the ten individuals; however, occult disease cannot be excluded.

Breast Cancer. Moderately raised MSA levels were detected in patients with Stage I and II active breast cancer (Table 1; Fig. 3). The mean level (±SE) of Stage I was 679 ± 86, with the MSA levels in Stage II being slightly higher at 946 ± 206 (not significant, $P = 0.205$). Using the cut-off value of 300 inhibition units, 72% of Stage I (n = 60) and 82% of Stage II (n = 50) had elevated levels. The range of values in both groups is shown in Fig. 3. Most are less than 1500 inhibition units. A greater proportion of patients with Stage III and IV breast cancer had raised levels of MSA, and the levels were, in general, higher than those found for the more localized disease (Table 1; Fig. 3). Highest levels of MSA were seen in patients with Stage IV breast cancer, with a mean of 3861 ± 322 inhibition units, and 87% (n = 142) of patients had elevated levels. The proportion of patients with an elevated MSA level, however, was not related to the site of metastases (data not shown). Stage III patients (75% with levels >300 inhibition units) did not differ significantly in the proportion of patients with elevated MSA levels when compared to Stage I and II patients; although the mean levels were higher this was not significant ($P = 0.353$ and $P = 0.980$, respectively) (1184 ± 315) (Table 1).

Patients previously diagnosed as having breast cancer (Table 1; Fig. 4), but with no clinical evidence of disease, or in remission, at the time of collection of the serum sample had raised MSA levels in 13 to 26% of cases. In particular, Stage IV patients in remission had a mean level of 681 ± 278 inhibition units, a level similar to that found in localized breast cancer. Also, of 31 Stage IV patients in remission, 8 had raised MSA levels (see Table 1 and Fig. 4) with 4 having high levels of >1000 inhibition units.

Benign Breast Disease. Elevated MSA levels were found in 7 of 40 (18%) patients with benign breast disease (Table 1; Fig. 4). Benign breast disease with raised levels included 3 patients with fibroadenoma (750, 378, 358 inhibition units), two with benign mammary dysplasia (303, 339 inhibition units), one with lobular hyperplasia (313 inhibition units), and another with cystic hyperplasia (352 inhibition units). In these patients the mean level of MSA was 157 ± 26, with a range of values from 50 to 750 inhibition units. This group is significantly different from normal females ($P = 0.002$) and from Stages I to IV of active breast cancer (see Table 1).

Other Malignant Tumors. MSA was detected in the serum of some patients with other malignant tumors (number examined = 213), but generally at lower levels than those found in patients with breast cancer (Fig. 5; Table 2). Elevated levels of MSA occurred in 1 of 12 patients with lung cancer, 5 of 26 patients with colon cancer, and 5 of 28 patients with lymphoma. Similarly, some patients with embryonic (1 of 7) and miscellaneous tumors (3 of 16) had raised levels of MSA, but this did not occur in the genitourinary tumors examined. There were 22% (2 of 9) of patients with high MSA levels and adenocarcinoma of unknown origin; these could conceivably have had breast cancer. Overall, 37 of 213 (17%) patients with other malignant tumors had raised levels of MSA.

Correlation of MSA Levels and Clinical Status: Monitoring the Progress of Breast Cancer

In a prospective study the MSA levels were determined in serum samples of 37 patients with metastatic breast cancer treated over 2- to 11-mo periods. Fig. 6 and Table 3 show the results of serial MSA testing arranged according to the clinical course. A change of 50% in MSA level was considered signifi-
Fig. 2. Distribution of MSA levels in the serum of apparently normal blood donors. Graph consists of a randomly selected population of 780 individuals from the total tested of 2406. Note that six individuals had levels of >500 inhibition units. These were 526, 766, 917, 1521, 1528, and 5283 inhibition units, respectively. I.U., inhibition units.

Fig. 3. Levels of MSA in the serum of patients with Stage I (1), II (2), III (3), and IV (4) active breast cancer determined by the competitive enzyme immunoassay. Each point represents an individual patient. The arbitrary cut-off value of 300 inhibition units is indicated by a horizontal line.

Fig. 4. Levels of MSA in the serum of patients with benign mammary conditions, and patients with previous breast cancer, but now with no evidence of disease (NED) or in remission via chemotherapy determined by the competitive enzyme immunoassay. [Their stage prior to operation/therapy is shown as Stage I (1), Stage II (2), Stage III (3), Stage IV (4).]

In total, 34 of 37 (92%) patients had changes in MSA levels which correlated with progression, stability, or regression of clinical disease. Only three patients (all of whom had soft tissue deposits only) had progressive disease but not significant change in MSA levels. In two of these patients with rapidly progressive disease, the MSA level gradually decreased until death 4 to 8 wk later. Postmortem examination in both cases revealed widespread metastases. All others with progressive disease showed increasing serum levels of MSA during the study period. In eight patients with clinically stable disease only small changes in MSA levels were observed. All 6 patients with regression of disease parameters had concomitant falling MSA levels.

Detailed serial measurements of MSA were performed in a number of patients in an attempt to correlate levels with clinical course. A representative example is described.

The patient (Fig. 7) had rapidly progressive metastatic breast cancer (bone, liver, lungs, local recurrence, contralateral breast, and axilla) and was treated with Adriamycin (from time 0 to 12 mo, see Fig. 7) with arrest of her disease progression and probable partial clinical response for a period of 4 mo. During that time, there was a corresponding fall in MSA level from 9,400 inhibition units to 929 inhibition units. However, over the following 8 mo, the MSA levels continued to rise to reach 10,000 inhibition units despite the fact that clinically and radiologically the disease remained stable, and it was not until
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8 mo later that disease progression was first clinically detected. The patient subsequently deteriorated rapidly and died within 4 wk from liver and renal failure.

Assay Parameters

The sensitivity and specificity of MSA levels in patients with Stages I and II were calculated and are presented in Table 4. It appears that MSA assay had a high sensitivity (84%) in patients with localized breast cancer and had good specificity (98%) in normal subjects; however, the false-positive rate (18%) in benign breast disease was moderately high.

DISCUSSION

A serum assay for breast cancer has been described, based on the detection of a high-molecular-weight glycoprotein (MSA) using the monoclonal antibody 3E1.2. The assay has shown that elevated levels of MSA are present in the serum of most patients with advanced breast cancer, and in a significant proportion of those with localized breast cancer compared to the normal adult population. In addition, these results have been confirmed by immunoblotting analysis of serum samples, showing increased levels in MSA in breast cancer patients. In contrast to previous reports (11), the antigen was successfully transblotted in this study, mainly due to improved techniques (17) and the use of 5% SDS-PAGE gel. The relationship of MSA to other circulating, high-molecular-weight glycoproteins such as human milk fat globule is currently under study.

The antibody 3E1.2 formed the basis of the competitive enzyme immunoassay used in this study. 3E1.2 has a reasonably specific tissue distribution, reacting with most breast cancers and to a lesser extent with normal breast epithelium and other normal tissues (11). The rationale behind the test was that larger volumes of tissue and increased expression found in breast cancer would be paralleled by increased levels of MSA in serum. Findings that patients with tumors unreactive with 3E1.2 by immunoperoxidase staining, such as colorectal cancer and lymphoma, have slightly elevated serum MSA levels would indicate that a mechanism of release for MSA is partially by necrosis or invasion of 3E1.2-reactive tissues by malignant cells. Whether a mechanism for active release of MSA is also functioning cannot be answered in this study.

The assay was formulated using a standard dilution of purified monoclonal antibody, as purified antigen was unavailable. Although not an optimal system, this method of standardization was shown to be reliable, with acceptable inter- and intraassay variations. As with the detection of other high-molecular-weight glycoproteins (4, 18), an arbitrary system of units was used, and no attempt was made to quantitate in terms of protein concentration, as the antigen appears to consist of predominantly carbohydrate and little protein (12). We were unable to

Table 3 Correlation of the clinical course and serum levels of MSA in breast cancer patients

<table>
<thead>
<tr>
<th>Clinical course</th>
<th>MSA level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regression</td>
<td>Stable</td>
</tr>
<tr>
<td>Decreased*</td>
<td>6</td>
</tr>
<tr>
<td>Unchanged*</td>
<td>0</td>
</tr>
<tr>
<td>Increased*</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
</tr>
</tbody>
</table>

* Decrease of more than 50%.
* Changing levels: increase of no more than 50% and decrease of less than 50%.
* Increase of more than 50%.
MSA LEVELS IN BREAST CANCER PATIENTS

Clinical course of a patient with advanced breast cancer

Fig. 7. Monitoring the clinical course of patients with MSA levels. Serial MSA levels were determined for a patient being treated for metastatic breast cancer. At the top of the graph, arrowheads indicate the commencement and termination of MSA testing. The thin line indicates the diagnosis of stable disease with probable partial response, and the bold line signifies a period of stable disease. P.D., progressive disease; S.D., stable disease; P.R., partial response. (See text for a more detailed description.)

Table 4 Assay parameters in patients with Stage I and II breast cancer compared to normal individuals and patients with benign breast cancer

<table>
<thead>
<tr>
<th></th>
<th>Breast cancer</th>
<th>Breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>benign breast</td>
<td>normals</td>
</tr>
<tr>
<td>Sensitivity*</td>
<td>84%</td>
<td>84%</td>
</tr>
<tr>
<td>Specificity*</td>
<td>92%</td>
<td>98%</td>
</tr>
</tbody>
</table>

* Stage I (n = 60), II (n = 50).

A number of other serum assays, using monoclonal antibodies, have been described for the detection of breast cancer-associated antigens and other tumor antigens (3–9, 18, 19). Comparing these assays to the competitive enzyme immunosay described in this study, a number of similarities and differences are found. (a) Although other monoclonal antibodies also detect epitopes present on the high-molecular-weight components of human milk fat globule membrane (5–7, 20), the epitope recognized by 3E1.2 is absent from both human milk and milk fat globule membranes (12), indicating a unique determinant. (b) MSA levels are raised in about 70 to 80% of patients with localized breast cancer, significantly greater than that reported for other markers, e.g., CA15-3, 18% (4); CEA, 9% (4); DCA, 33% (9); MAM-6, 23% (5); and W1, 0% (7). (c) Low levels of MSA in colorectal and pancreatic cancer distinguish this assay from other high-molecular-weight antigens like CEA (4), DU-PAN-2 (18), and Ca19-9 (19).

In this study no individual with breast cancer was found in the testing of over 2000 blood donors, half of whom were female. Only 10 of 46 blood donors with levels of >300 inhibition units could be examined for evidence of occult lesions. None was found with breast cancer; however, given that the standardized rate of breast cancer in the area of collection is 0.6 of 1000, a considerably larger population would be required to find patients with early disease. Whether MSA levels will be a useful adjunct for screening normal populations is a question for a larger study. The assay can detect about 3 of 4 patients who would typically be detected in a screening program (i.e., Stage I and Stage II breast cancer). However, this must be considered in the context of the 25% false-negative rate, 18% of false-positives in subjects with benign breast disease, and a similar false-positive rate in other malignancies and nonmalignant disorders (12). We are currently using the assay on subjects undergoing mammography to determine if MSA testing (logistically simpler and cheaper) will help in the selection of subjects for mammography.

This study has shown that levels of MSA are elevated in patients with localized and advanced breast cancer. In contrast, normal individuals and patients with benign breast disease and other cancers have, on average, much lower antigen levels. Our findings indicate that MSA levels are useful for monitoring the clinical course of patients with known breast cancer. Whether MSA levels could be useful with other parameters to aid in the early diagnosis of breast cancer will ultimately be determined by larger studies.

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