Immunohistochemical Localization of Parathyroid Hormone-related Protein in Human Breast Cancer


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ABSTRACT

Parathyroid hormone-related protein (PTHrP) is known to be a causative factor in humoral hypercalcemia of malignancy. A polyclonal rabbit antiserum directed against the amino-terminal region of the protein and immunoperoxidase methods have been used to detect the presence of PTHrP in a series of 102 consecutive invasive breast tumors removed surgically from normocalcemic women. Positive PTHrP staining was detected in 60% of the tumors but not in the accompanying normal breast tissue. Positive staining was related to the progesterone receptor status of the tumor (P = 0.039) and to the prognostic index of the patient (P = 0.046) and not to estrogen receptor status, patient age, tumor size, histological grade, or nodal status.

INTRODUCTION

Hypercalcemia is a common complication of cancer. Malignancy-associated hypercalcemia may arise due to the tumor metastasizing to bone where it causes localized destruction of the bone (1). Alternatively, the tumor may release a humoral factor which acts on bone to promote increased bone resorption and on kidney to restrict calcium excretion. This syndrome of hypercalcemia in the absence of bone metastases has been termed HHM (2). The features of HHM resemble those of primary hyperparathyroidism, including increased bone resorption, decreased calcium excretion, and increased nephrogenous cyclic AMP and phosphate excretion (3–5), which suggested that the syndrome may be caused by the tumor producing a factor that acts like PTH. When the factor responsible for HHM was purified, cloned, and sequenced it was found that, while similar to PTH in many respects, this protein was structurally and immunologically distinct from PTH (6–8). PTHrP has an amino-terminal sequence very similar to that of PTH, with 8 of the first 13 amino acids identical, which are sufficient to permit PTHrP to interact with PTH receptors to produce its PTH-like effects. Studies of the synthetic peptide PTHrP(1–34) show that it is capable of producing PTH-like effects (9, 10), and antisera to PTHrP are able to reduce the elevated serum calcium levels in athymic mouse models of HHM (11).

Breast cancer is the malignancy most commonly associated with hypercalcemia (12). Breast tumors frequently metastasize to bone, and hypercalcemia in breast cancer has been attributed to skeletal metastases rather than to a humoral mechanism (1, 2). Evidence that breast cancer may be associated with HHM in some patients came from studies by Kimura et al. (13) and Percival et al. (14). Isales et al. (15) reported that 24% of the breast cancer patients studied had hypercalcemia without bone metastases and that a humoral mechanism for the hypercalcemia may have been operative in as many as 53% of the patients. Furthermore, Coleman et al. (16) found that 15% of hypercalcemic breast cancer patients had no bone metastases. This suggestion that breast cancer may be associated with HHM was supported by the isolation of PTHrP from a breast tumor by Burtis et al. (17).

Immunohistochemical methods have been used to detect the presence of PTHrP in several different types of tumors including squamous cell carcinomas and renal carcinomas, tumors commonly associated with HHM (18). In the present study, immunoperoxidase procedures, using an antiserum directed against the amino-terminal region of the PTHrP molecule, were used to locate its presence in a series of breast tumors and to determine the incidence of PTHrP staining in breast tumors.

MATERIALS AND METHODS

Patients

The tumors in this study came from 102 women with invasive breast cancer who presented consecutively to the University Department of Surgery Breast Unit at St. Vincent's Hospital, Melbourne, Australia from August 1987 to March 1989. All patients were included regardless of history or stage. The following information was entered on a computerized database.

Prognostic Factors. Age, tumor size (mm), histological type, histological grade [according to the method of Bloom and Richardson (19)], pathological nodal status and AJCC stage (20), ER and PR levels, and PI scores. The hormone receptor levels were determined by the method described by Mercer et al. (21). Tumors containing hormone receptor levels >10 fmol/mg protein are considered to be ER or PR positive. Tumors with hormone receptor levels <5 fmol/mg protein are considered to be ER or PR negative. For levels between 5 and 10 fmol/mg protein results are considered equivocal, although in clinical practice levels <10 fmol/mg protein are considered to be negative. This breakpoint between positive and negative receptor status is widely used clinically in assessing patient response to hormonal therapy and overall survival (21–23). Prognostic index scores were calculated for patients with AJCC stage 1–3 breast cancer using the formula PI = N + E + P + A where N = 0 if no nodes are involved, 13 if 1–3 nodes are involved, 31 if >3 nodes are involved; E = 15 if ER <10 fmol, 0 otherwise; P = 12.5 if PR <10 fmol, 0 otherwise; and A = number of years over 65. This index was developed by Bryan et al. (24) and validated by Alexander et al. (25). In addition, one extra pathological feature was assessed, namely, the degree of intratumoral calcification, which was graded subjectively as absent, low, or high.

Clinical Factors. Local recurrence, distant recurrence, site of first metastasis, pattern of metastases, symptomatic hypercalcemia.

Blood Chemistry. Corrected calcium, phosphate, aspartate transaminase, alkaline phosphatase, γ-glutamyl transpeptidase, carcinoembryonic antigen.

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3 J. A. D. is the recipient of an Australian Research Council Individual Fellowship.
4 To whom requests for reprints should be addressed.
5 The abbreviations used are: HHM, humoral hypercalcemia of malignancy; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related protein; AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor; PI, prognostic index; PBS, phosphate buffered saline; NCS, newborn calf serum; PAP, peroxidase-antiperoxidase.

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Eighty-four women presented with AJCC stage 1–3 cancers (group A), 7 with stage 4 disease (group B), and the remaining 11 had local recurrence from a previously treated breast cancer ± distant metastases (group C). Of the 91 patients who did not present with a local recurrence, 78% had a mastectomy (4 with omentoplasty), 20% had breast conservation, and 2% had biopsy alone. In addition, 85% had an axillary clearance. Patients considered to have a high risk of recurrence were given adjuvant chemotherapy (25%), tamoxifen (29%), and radiotherapy (25%).

Tumor Samples

The tumor tissue was fixed in 10% buffered formalin for 12–24 h, processed according to routine procedures, and then embedded in paraffin blocks. Sections 5 μm thick were cut on a Leitz 1515 rotary microtome, adhered to glass microscope slides, and dried in a 37°C oven overnight.

Antiserum

The antiserum used in this study was a polyclonal antiserum against the synthetic peptide PTHrP(1–34). The antiserum (394.7) was raised in New Zealand white rabbits and its specificity has been well characterized. The antiserum shows no detectable cross-reactivity with PTH in radioimmunoassay (26), on Western blots, or in blocking biological activity, even at high antiserum concentrations comparable to those used in the present study (18, 27). This antiserum has been used extensively in immunohistochemistry (18, 28).

Immunohistochemical Staining

The PAP method of tissue antigen detection was a modification of that of Sternberger et al. (29) as described by Danks et al. (18). The tissue sections were dewaxed in two changes of xylene and placed in absolute ethanol for 1 min before being immersed in methanol with 1% hydrogen peroxide for 30 min to block endogenous peroxidase activity in the tissue (29). After three 1-min washes in PBS, the sections were covered with a 1:10 dilution of normal swine serum in 5% NCS (Commonwealth Serum Laboratories, Melbourne, Australia) in PBS and incubated for 30 min in order to reduce background staining (30). Excess normal swine serum was drained, and the sections were incubated with the primary rabbit antiserum, anti-PTHrP(1–34), for 1 h at 25°C. The antiserum was used at dilutions of 1:25 and 1:50, made up in 5% NCS in PBS. Following these 10-min washes in 5% NCS in PBS to remove any unbound antiserum, the sections were incubated with a 1:40 dilution of swine anti-rabbit immunoglobulins (Dakopatts, Glostrup, Denmark) in 5% NCS in PBS for 30 min. This was followed by two 5-min washes in 5% NCS in PBS and one 5-min wash in PBS. The soluble horseradish peroxidase and rabbit antihorseradish peroxidase complex (Dakopatts), diluted to 1:80 in PBS, was applied for 30 min, after which the sections received three 5-min washes in PBS. The slides were then immersed in a solution consisting of 200 ml 0.05 M Tris (pH 7.6) with 100 mg 3,3'-diaminobenzidine tetrahydrochloride (Sigma Chemical Company, St. Louis, MO) and 0.15% hydrogen peroxide for 7 min. After three 5-min washes in distilled water, the sections were counterstained with Mayer's hematoxylin (Sigma), dehydrated through increasing concentrations of ethanol, and mounted in dibutylphthalate xylene.

Controls

To ensure that the staining observed was specific for PTHrP, several methods and antibody controls were performed: (a) alternating deletion of the antibody layers (primary antiserum, secondary antiserum, PAP complex); (b) preabsorption of the anti-PTHrP(1–34) antiserum with 0.5 mg/ml PTHrP(1–34) overnight at 4°C; (c) application of 0.5 mg/ml PTHrP(1–34) to the tissue sections 5 min before the addition of the anti-PTHrP(1–34) antiserum.

Included in each assay were the following two controls: (d) positive control (squamous cell carcinoma of the skin) and (e) replacement of the anti-PTHrP(1–34) antiserum with non-immune rabbit serum.

Evaluation of Immunohistochemical Staining

The criteria used in assessing the immunoperoxidase staining of the breast tumors were as follows.

Positive/Negative. Tumors were called positive for PTHrP if any of the tumor cells were stained brown. Tumors were called negative for PTHrP if no brown staining of tumor cells was observed.

Intensity of Staining. The intensity of staining of the tumors was graded on a scale of 0–3, where 0 = no positive staining of tumor cells; 1 = weak positive staining; 2 = moderately strong positive staining; 3 = strong positive staining of tumor cells.

Type of Staining. Two patterns of staining of tumor cells were observed, a cytoplasmic pattern and a vesicular pattern. In the cytoplasmic pattern there is diffuse brown staining of the cytoplasm of the cell. The second pattern of staining was described as vesicular because it appeared to be associated with vesicles or vacuoles in the cytoplasm of the cell and resulted in irregular staining of the cell. Some tumors showed both patterns of staining and were described as having a mixed pattern of staining.

Area of Staining. An estimate of the percentage of cells in the section which stained positively was made using a scale of 1–4, where 1 = 0–5% of tumor cells positive; 2 = 6–25%; 3 = 26–50%; 4 = >50% of tumor cells positive.

Statistical Analysis

Frequency data were analyzed with the χ² test and the Fisher exact test when numbers were <20. Means were compared with Student's t test. The data were analyzed using the SPSS Program (SPSS Inc., Chicago, IL).

RESULTS

Immunohistochemical Staining for PTHrP. Of the 102 tumors, 61 tumors exhibited positive staining with the anti-PTHrP(1–34) antiserum. A cytoplasmic staining type was the commonest pattern, accounting for 36 tumors (59%). A vesicular pattern was present in 15 cases (25%) and the remainder (16%) showed a mixed pattern. Examples of these staining patterns are shown in Figs. 1 and 2. In general, the invasive component of the tumor stained more strongly that the intraductal component. Microlcification was often associated with areas of positive tumor staining (Fig. 3). Positive PTHrP staining was not observed in residual normal duct epithelium (Fig. 3) or in breast epithelial elements in associated fibrocystic disease.

Positive staining for PTHrP was found in 58% of group A, 71% of group B, and 64% of group C. The intensity of staining was weak in 42 tumors (69%), moderate in 17 (28%), and strong in 2 (3%). The area of staining was <5% in 11 tumors (18%), 6–25% in 26 tumors (43%), 26–50% in 16 tumors (26%), and >51% in 8 tumors (13%). When staining intensity and area of staining were combined as the staining index, it was found to be weak for 32 tumors (52%), moderate for 16 (26%), and strong for 13 tumors (21%). There were no significant differences in the staining characteristics among the three groups. The staining characteristics for the 102 breast tumors are summarized in Table 1.
Fig. 1. Invasive breast duct carcinoma showing the cytoplasmic pattern of staining. PTHrP(1–34) immunoperoxidase; × 800.

Fig. 2. Breast carcinoma exhibiting the vesicular staining pattern. Normal breast duct does not stain. PTHrP(1–34) immunoperoxidase; × 250.
Fig. 3. Intraductal breast carcinoma with microcalcification (arrow) showing positive staining for PTHrP(1–34). PTHrP(1–34) immunoperoxidase; × 250.

Fig. 4. Non-immune serum control of Fig. 3. showing an absence of staining for PTHrP(1–34). Arrow, area of calcification. PTHrP(1–34) immunoperoxidase; × 125.
Relationship between Tumor PTHrP Staining and Clinical Factors. Seventeen patients (20%) in group A have so far developed recurrent disease (6 combined local and distant relapse, 6 local relapse alone, and 5 distant relapse alone). Of the 11 patients with distant relapses, 7 patients have developed bone metastases, 5 of whom had positive-staining primary tumors. In contrast, none of the 4 patients who developed nonosseous metastases had a primary tumor which stained positively for PTHrP (Fisher exact test, $P = 0.06$). Three patients have subsequently developed symptomatic hypercalcemia and all 3 had positive-staining primary tumors.

DISCUSSION

Positive PTHrP staining was detected in 60% of the breast tumors in this study; it was significantly related to PR status for groups A and B and to prognostic index for group A alone (Table 2). PR status and prognostic index are known to be related to the survival of the patient, with a positive PR status and a low PI value being favorable for survival (24). Improved prognosis is associated with the presence of hormone receptors

Table 1 Staining characteristics of 102 breast tumors with anti-PTHrP(1–34) antiserum

<table>
<thead>
<tr>
<th>Anti-PTHrP antiserum</th>
<th>Group A (n = 84)</th>
<th>Group B (n = 7)</th>
<th>Group C (n = 11)</th>
<th>Total (n = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive staining</td>
<td>49*</td>
<td>5</td>
<td>7</td>
<td>61</td>
</tr>
<tr>
<td>Negative staining</td>
<td>35</td>
<td>2</td>
<td>4</td>
<td>41</td>
</tr>
</tbody>
</table>

Intensity of staining

<table>
<thead>
<tr>
<th>Type of staining</th>
<th>Group A (n = 84)</th>
<th>Group B (n = 7)</th>
<th>Group C (n = 11)</th>
<th>Total (n = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytoplasmic</td>
<td>29</td>
<td>3</td>
<td>4</td>
<td>36</td>
</tr>
<tr>
<td>Vesicular</td>
<td>11</td>
<td>2</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Mixed</td>
<td>9</td>
<td>0</td>
<td>1</td>
<td>10</td>
</tr>
</tbody>
</table>

* Number of tumors.

Controls. Positive PTHrP staining was not detectable in the sections in which the primary antiserum, secondary antiserum, or PAP complex was omitted from the staining sequence. Preabsorption of the anti-PTHrP(1–34) antiserum with PTHrP(1–34) overnight and application of PTHrP(1–34) to the tissue sections 5 min before the addition of the anti-PTHrP(1–34) antiserum both significantly reduced the amount of staining observed in normal skin; in tumor sections the preabsorption abolished positive staining. If positive staining occurred in the breast sections which received the non-immune rabbit serum instead of the primary antiserum, it was considered to be nonspecific, as were the corresponding areas in the breast sections which did receive the primary antiserum. This nonspecific staining occurred in fewer than 5% of the sections studied.

A similar staining result is seen in those tumor sections which received the preabsorption treatment. After taking these results for the control procedures into account, we considered positive staining observed in the experimental sections to be specific for PTHrP.

Relationship between PTHrP Staining and Prognostic Factors. The relationship between positive PTHrP staining and a number of factors known to be associated with survival for groups A and B is summarized in Table 2. Group C is omitted from these considerations because of previous exposure to radiation and chemotherapy. The 57 group A patients who had an evaluable St. Vincent’s Hospital prognostic index score were subdivided into high and low risk groups based on a prognostic index score cutoff of 27. This cutoff point of ≤27 was chosen because patients with this prognostic score have approximately ≥80% probability of surviving 5 years. Of the 29 patients defined as low risk, 21 had primary tumors staining positively for PTHrP, while of the 28 high risk patients, 13 had tumors positive for PTHrP ($\chi^2 = 4.0, P = 0.046$). Positive PTHrP staining was not related to the age of the patient, grade of the tumor, ER status, histology, AJCC stage, lymph node status, tumor size, or calcification.

Table 2 Relationship among staining with anti-PTHrP(1–34) antiserum, prognostic factors, and intratumoral calcification (groups A and B combined)

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Positive (n = 54)</th>
<th>Negative (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (n = 91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 yr</td>
<td>18*</td>
<td>12</td>
</tr>
<tr>
<td>&gt;51 yr</td>
<td>36</td>
<td>25</td>
</tr>
<tr>
<td>Mean size (mm) ± SD (n = 91)</td>
<td>34 ± 19</td>
<td>42 ± 25</td>
</tr>
<tr>
<td>Histological type (n = 91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infiltrating ductal</td>
<td>29</td>
<td>15</td>
</tr>
<tr>
<td>Infiltrating ductal + ductal carcinoma in situ</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>Infiltrating lobular</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Macinuous</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Tubular/papillary/cribriform</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Histological grade (n = 85)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>II</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>III</td>
<td>26</td>
<td>19</td>
</tr>
<tr>
<td>Pathological nodal status (n = 77)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No nodal involvement</td>
<td>21</td>
<td>13</td>
</tr>
<tr>
<td>1–3 positive nodes</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>&gt;3 positive nodes</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>AJCC stage (n = 91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>II</td>
<td>26</td>
<td>20</td>
</tr>
<tr>
<td>III</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Estrogen receptor status (n = 87)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative (&lt;10 fmol/mg protein)</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Positive (&gt;10 fmol/mg protein)</td>
<td>35</td>
<td>19</td>
</tr>
<tr>
<td>Progesterone receptor status (n = 76)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative (&lt;10 fmol/mg protein)</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>Positive (&gt;10 fmol/mg protein)</td>
<td>32</td>
<td>17</td>
</tr>
<tr>
<td>Tumor calcification (n = 91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>23</td>
<td>21</td>
</tr>
<tr>
<td>Low</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>High</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

* Number of tumors.

a Missing values in groups A and B: Precise assessment of tumor grade was not possible in 6 of 91 tumors; pathological nodal status was not available in the 14 of 91 patients in whom no nodal dissection was performed; ER status in 4 of 91 and PR status in 15 of 91 was not determined either because of insufficient fresh frozen material for analysis or due to technical faults in the assay.

b $P = 0.039$. 

c $P = 0.046$. 

d $\chi^2 = 4.0$.
and appears to be independent of nodal status. Progesterone receptor levels have been reported to be a stronger predictor of outcome than estrogen receptor levels (32). These patients will be followed up and analyzed at 5 and 10 years to see whether positive PTHrP staining is related to a disease-free state and overall survival.

Although it is too early in the follow-up to make any definite statement, from the 17 patients who have so far developed recurrent disease, the pattern of relapse seems to suggest that, if a positive-staining tumor metastasizes, it does so to bone. Because of the suggestion by Coleman et al. (16) that there is an association between the presence of liver metastases and the development of hypercalcemia in breast cancer patients, it will also be relevant to investigate the pattern of liver metastases in the patient follow-up.

Positive PTHrP staining was found in 60% of the tumors studied but the patients were normocalcemic at the time of surgery. This is consistent with results of a study by Danks et al. (18) which detected PTHrP by immunoperoxidase methods in 100% of the squamous cell carcinomas studied, although none of the patients from whom the tumors were taken was hypercalcemic. This may be explained by the fact that, while the immunohistochemical staining indicates the presence of PTHrP in the tumor cells, it gives no indication as to whether the PTHrP is actually secreted into the circulation. In addition, hypercalcemia would only occur if the production and secretion of PTHrP were sufficient to overcome the normal homeostatic mechanisms controlling calcium metabolism. Therefore, before it can be said with any certainty that some breast tumors secrete PTHrP which then causes hypercalcemia, a validated, sensitive assay is required for detecting the levels of PTHrP in the circulation. It is of interest that the three patients who have since developed symptomatic hypercalcemia during follow-up have all had positive-staining tumors.

Of the 47 tumors with calcification, 31 (66%) stained positively for PTHrP (Table 2). It was noted that there was an association between tumor calcification and a vesicular pattern of staining which was significant (P = 0.04) even though the overall relationship between tumor calcification and PTHrP staining is not clear. Since PTHrP is associated with calcium metabolism, a relation between tumor calcification and PTHrP staining is an interesting observation. It could suggest that the PTHrP of the tumor cells is having a local effect on calcium transport, leading to localized deposition of calcium in the region of the positive tumor cells.

In some tumors the invasive component of the tumor was positive for PTHrP, while the intraductal component was negative or only weakly positive; also, marginal cells of tumor cell clumps were positive, while the central cells were negative. Hoekman et al. (33) found that the production of PTHrP by squamous carcinoma cells is modulated by an interaction with fibroblasts. A similar mechanism may be operating in the breast tumors; those marginal and invasive tumor cells in proximity to the fibroblasts of the surrounding stroma are able to produce PTHrP, while the central and intraductal cells, without this interaction, are unable to produce the protein.

The immunohistochemical detection of PTHrP in the cytoplasm of breast tumor cells strongly suggests that these cells are synthesizing the PTHrP. However, the immunohistochemical staining is only a reflection of the interaction of anti-PTHrP antibodies with PTHrP and thus gives no information concerning whether the PTHrP was actually synthesized by those cells or acquired from some other source. The way to resolve this would be to use Northern analysis or in situ hybridization techniques to determine whether the cells possess the mRNA for PTHrP. Northern analysis of two breast tumors associated with HHM (34) revealed the presence of PTHrP mRNA in these tumors, indicating that breast tumors are capable of synthesizing PTHrP.

Although in this study we did not note PTHrP staining in any accompanying normal breast tissue, nevertheless it is clear that a significant proportion of breast cancers contain PTHrP. It is of interest to note that the lactating breast has been shown to possess PTHrP mRNA (35) and also that PTHrP is found in considerable amounts in the milk of several mammalian species including man (36, 37). Production of PTHrP by breast carcinomas may reflect resumption by the tumor cells of properties of activated breast epithelium. The exact pathological significance remains to be elucidated. We have noted in this study of 102 patients a correlation between positive PTHrP staining in tumors and a favorable prognostic index. If this relationship is maintained in studies of larger numbers of patients, it may be consistent with a role of PTHrP in promoting tumor cell differentiation.

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