Oestrogen and progesterone receptor expression in mammary fibromatosis

S A Rasbridge, C E Gillett, R R Millis

Abstract

Aims—To investigate the oestrogen and progesterone receptor concentrations expressed on mammary fibromatoses to determine their responsiveness to oestrogenic stimuli.

Methods—Six mammary fibromatoses were examined using immunohistochemistry for the presence of oestrogen and progesterone receptors using antibodies against the receptor proteins. Enzyme immunoassays (EIAs) using the same antibodies were also performed in four patients. Immunohistochemical staining for pS2 protein was also carried out as a measure of functional oestrogen receptors.

Results—Neither receptor nor pS2 protein was expressed using immunohistochemistry. Very low concentrations of both oestrogen and progesterone receptors were shown by EIA.

Conclusion—These results indicate the absence of clinically important concentrations of oestrogen and progesterone receptors in breast fibromatoses and suggest that treatment directed against oestrogen is unlikely to be beneficial.

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Fibromatoses are well recognised, benign, but locally infiltrative lesions which have been described in many different soft tissues. They are rare in the breast, most examples having been reported of one or two cases, until the recent publication of three larger series totalling 67 patients. Problems that may arise in patients with mammary fibromatosis are those of incorrect diagnosis as a malignancy and the possibility of local recurrence with progressive infiltration of local structures. The aetiology of these lesions is largely unknown, but there is interesting preliminary evidence that some cases may be hormonally driven. For instance, abdominal fibromatoses commonly arise in women during their reproductive years and grow vigorously during pregnancy. There have been reports of a dramatic clinical response of pelvic and abdominal lesions to the anti-oestrogen drug tamoxifen. And there have also been some reports of oestrogen and progesterone receptor positivity in fibromatoses, including one case in the breast.8–10

We undertook an immunohistochemical study of the oestrogen and progesterone receptor content of six cases of mammary fibromatosis; in four cases EIA results were also available. Immunohistochemical staining for pS2, a 6.4 kilodalton protein inducible by oestrogen was also carried out. Positive pS2 staining has been reported to be predictive of an enhanced response to tamoxifen in breast carcinoma and to have prognostic value.11–12

Methods

Six patients attending the Breast Clinic of the ICRF Clinical Oncology Unit at Guy's Hospital between 1978 and 1991 were diagnosed as having a fibromatosis. Five presented with a palpable mass clinically suspicious of a carcinoma; two of the masses were located within the axillary tail of the breast. The sixth woman had a breast lesion detected on mammographic examination as part of the national screening programme but was asymptomatic. Further clinical details are given in the table.

Formalin fixed, paraffin wax embedded sections were stained with antibodies to oestrogen receptor (H222; Abbott Laboratories, Chicago, USA), progesterone receptor (KD68; Abbott) and pS2 protein (CIS biointernational, GIF-sur-Yvette, France) using a standard peroxidase conjugated streptavidin–biotin technique. To demonstrate the presence of oestrogen receptors the sections

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Clinical details of patients with mammary fibromatosis

<table>
<thead>
<tr>
<th>Case No</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<tr>
<td>Age (y)</td>
<td>30</td>
<td>20</td>
<td>34</td>
<td>27</td>
<td>53</td>
<td>56</td>
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<tr>
<td>Site</td>
<td>Supra-areolar Right breast</td>
<td>Upper outer quadrant Right breast</td>
<td>Periareolar Right breast</td>
<td>Axillary tail Left breast</td>
<td>Axillary tail Left breast</td>
<td>Lower outer quadrant Right breast</td>
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<tr>
<td>Symptoms</td>
<td>Breast lump</td>
<td>Breast lump</td>
<td>Breast lump</td>
<td>&quot;Breast&quot; lump</td>
<td>&quot;Breast&quot; lump</td>
<td>Asymptomatic</td>
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<tr>
<td>Clinical size</td>
<td>0.5 cm</td>
<td>1.2 cm</td>
<td>2 cm</td>
<td>9-0 cm</td>
<td>4-5 cm</td>
<td>0.8 cm (on x-ray)</td>
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<tr>
<td>Mammmography</td>
<td>Not done</td>
<td>Not done</td>
<td>Not done</td>
<td>Not done</td>
<td>Not done</td>
<td>Spiculated tissue density</td>
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required prior treatment with Pronase E for 9 minutes to expose the antigen. Antibodies to both the receptors were incubated with the sections overnight at room temperature; pS2 could be detected after incubation for 1 hour. Fresh tissue was snap-frozen in liquid nitrogen and homogenised in a tissue homogeniser. Cytosol fractions were prepared by extraction in TRIS/EDTA/sodium molybdate buffer and centrifugation at 4°C. An EIA kit from Abbott Laboratories was then used to assay oestrogen and progesterone receptors.

Results

Four patients were premenopausal; none was pregnant or taking oral contraceptives at the time of diagnosis, although three patients had used oral contraceptives between nine and four years previously. A fifth woman had undergone a bilateral salpingo-oophorectomy 14 years earlier without receiving any hormonal replacement therapy. Follow up of four patients at between one and 11 years showed no recurrence. One woman had a recurrence of her lesion within two years but no further problems for seven years after a second resection. The remaining patient was lost to follow up after her initial treatment.

The macroscopic appearances of the lesions varied: in two cases the specimen showed firm but otherwise unremarkable fibro-fatty breast tissue without a discrete mass. In the others a contracted, firm, pinkish-white, stellate mass resembling a small carcinoma was apparent within otherwise fatty tissue.

Light microscopic examination of each case showed a poorly circumscribed lesion composed of spindle shaped fibroblasts surrounded by coarse bands of rather hyaline collagen. The fibroblastic proliferation had an infiltrative edge extending into the fatty stroma and entrapping the normal structures of the breast when these were present. Neither mitotic activity nor cellular atypia was seen (fig 1).

Immunohistochemical staining for oestrogen and progesterone receptors was negative in all cases (fig 2A), despite good positive controls and occasional positive nuclei within breast ductal epithelial cells adjacent to some fibromatoses (fig 2B). No staining for pS2 was seen in either the fibromatoses or in normal breast tissue, but a control mammary carcinoma specimen was clearly stained.

EIA of oestrogen receptor content in four cases (2, 4, 5 and 6) gave values of between 5 fmol/mg and 7 fmol/mg (of cytosol protein) with progesterone receptor concentrations between 0 fmol/mg and 9 fmol/mg.

Discussion

The aetiology of fibromatoses is unknown. Physical, hormonal, and genetic factors have been implicated. These are not necessarily mutually exclusive as a combination of factors may be involved. The aetiological factors may
Oestrogen and progesterone receptor expression in mammary fibromatosis
differ in the different subgroups of fibromatosis.

The breast is responsive to female sex hor-
mones—its development depends on oestro-
gen and even the mature breast undergoes
cyclical epithelial and stromal changes in
response to hormonal fluctuations during the
menstrual cycle.13 14 The proliferative activity of
epithelial cells has been shown to vary with
changing concentrations of oestrogen and
progesterone, but little is known about the
regulation of proliferation in stromal cells.15
Strongly positive immunostaining for proges-
terone receptors, however, has been observed in
the hyperplastic stromal reaction known as
pseudoangiomatous hyperplasia,16 especially
when arising independently of mammary
hamartomas. There is therefore some support
for the suggestion that proliferation of breast
stromal cells is hormonally regulated.

There are reports of clinical responses to
“anti-oestrogen” treatment (testolactone or
tamoxifen) in patients with abdominal wall or
pelvic fibromatoses, with occasionally dra-
matic results.4-7 Assay of receptor content
from 10 such masses has shown either nega-
tive results or very low receptor concentra-
tions: specifically, five cases had detectable
oestrogen receptor concentrations of 0·03 and
4·6 fmol/mg. In two cases progesterone
receptor concentrations of 9·4 and 0·2
fmol/mg were found.89 Conflicting results
have been seen, however, in the only two
cases of mammary fibromatosis examined.
One was associated with high progesterone
receptor concentrations of 74 fmol/mg and
oestrogen receptor concentrations of 10
fmol/mg10; another group found that their
case was completely negative for both recep-
tors.7

In view of the contradictory evidence we
were prompted to investigate the receptor sta-
tus of our cases of breast fibromatosis. All six
cases were negative for oestrogen and progres-
terone receptors as judged by immunostain-
ing. Although the antibodies used were
originally used in frozen sections, recent
changes in methodology have allowed them
to be used in fixed tissue with reliable results,
comparable with those seen in frozen tissue.17 18 Several studies have shown an
85–95% correlation between the results of
biochemical assays and immunohistochemical
staining of both receptors.17 18 In our four
cases, where suitable material was available,
the EIA showed low but detectable concen-
trations of receptors. In our laboratory, had
these levels been present in a breast carcino-
ma, they would have been regarded as “negat-
ive” insofar as they predicted a likely
response to endocrine treatment.

The cytoplasmic stain for pS2 is induced by
exposure to oestrogen and although of
unknown function, has been associated with
an enhanced response to tamoxifen in breast
carcinoma even in oestrogen receptor nega-
tive tumours.11 12 pS2 may therefore be a
marker of a functional oestrogen receptor
which does not express the normal progesterone
detected by the H222 antibody. In case the
putative receptors on fibromatosis were of
this nature we stained for pS2 protein. This,
again, was negative in all cases.

These results indicate that if oestrogen and
progesterone receptors can be found in mam-
mary lesions, the concentrations are usually
low and suggest that anti-oestrogen treatment
is unlikely to be of benefit. However, other
mechanisms such as induction of transform-
ing growth factor β1,7 which can act as a
potent growth inhibitor, may underlie the
reported responses to tamoxifen.

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