Breast Inflammatory Gigantomastia in a Context of Immune-Mediated Diseases


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Context: Localized breast lesions have been described in lupic or diabetic patients. However, the description of breast gigantomastia in women presenting with autoimmune diseases has not been reported.

Setting: The study took place within the Department of Endocrinology and Reproductive Medicine, Necker Hospital, Paris, France.

Patients: We describe eight patients with inflammatory gigantomastia, occurring in a context of immune-mediated diseases: myasthenia, chronic arthritis, or thyroiditis.

Main Outcome Measures: Together with hormonal, immunological, and breast magnetic resonance imaging (MRI) evaluation, breast histology enabled us to perform immunocytochemical and indirect immunofluorescence studies. Control sera were obtained from patients with (n = 10) and without (n = 7) antinuclear antibodies.

Results: Six of the eight patients developed gigantomastia either at puberty or during pregnancy. Neither a hormonal oversecretion nor a specific immunological pattern was observed. All patients except one presented antinuclear antibodies. Histological study revealed a diffuse, stromal hyperplasia and a severe atrophy of the lobules. A rarefaction of adipocytes was also noted, as previously suggested on MRI. There was a perilobular lymphocytic infiltrate made of CD3+ lymphocytes. Study of sera from five of six cases of gigantomastia showed a nuclear immunofluorescence pattern in normal mammary ductal and lobular glandular epithelium, as well as in kidney and intestine epithelial cells. In control sera, a nuclear signal was observed only when antinuclear antibodies were present.

Conclusions: We suggest that breast tissue may be a target tissue in autoimmune diseases, this process being favored by the hormonal milieu. However, the precise mechanism of such association is not individualized. The fact that stromal hyperplasia is the main histological feature justifies the search for the involvement of growth factors in such a process. (J Clin Endocrinol Metab 90: 5287–5294, 2005)

Breast diseases are very heterogeneous in their presentation and their mechanisms, and although breast cancer remains the obsession of every clinician, most breast diseases are benign (1–3). On occasion, clinicians may observe strong proliferative patterns of the breast such as juvenile hypertrophy, marked by an extremely sudden and homogeneous increase of breast volume, leading to physical and psychological complications (4–6). The pathogenesis of such diseases remains poorly understood; however, the onset of such clinical disorders at puberty or during pregnancy highlights the potential role of sex steroids (7–9).

Breast tissue is also a potential target tissue in certain autoimmune diseases. In diabetes or lupus, mastitis is described, marked by pseudotumoral lesions and a lymphocytic infiltration of the breast parenchyma but without increase of breast volume (10–13). Such a description has been called sclerosing lymphocytic lobulitis (14, 15) or lymphocytic mastopathy (16).

The observation of breast hypertrophy in patients presenting with autoimmune diseases has not been clearly studied. Here, we present eight cases of women who had developed a rapid and significant breast hypertrophy, with inflammatory skin symptoms and in a context of autoimmune or immune-related disease. We present the clinical, hormonal, immunological, radiological, and histological data and discuss various hypotheses for the mechanisms underlying this condition.

Patients and Methods

Eight patients have been studied. Two of them developed gigantomastia during pregnancy, four at the onset of puberty. In the last two cases, no promoting event was observed, except the d-penicillamine treatment in one of them. All patients, or their parents, signed an informed consent form for blood sampling and breast biopsy.

Concerning the two cases that occurred during pregnancy, both patients presented with myasthenia, previously undiagnosed in patient 1 and already treated in patient 2. Chest circumference progressively increased, reaching in patient 2 132 cm at 8 months of pregnancy (Fig. 1, left). Various treatments were initially proposed (dopamine agonists and local and systemic progesterone), but these were unsuccessful, and insufficient to stop the increase in chest circumference. As it continued to increase, with marked signs of local inflammation, prednisolone (0.5 mg/kg per day) was started. This treatment led to a rapid regression of the breast hypertrophy, with a decrease in chest circumference and attainment of normal values before delivery.

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Abbreviations: Δ4, Δ4-Androstenedione; E1, estrone; ER, estradiol receptor; HLA, human leukocyte antigen; MRI, magnetic resonance imaging; PRL, prolactin.

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mg/kg/d) was initiated, permitting a stabilization of the symptoms during pregnancy. Six months later, given the major breast volume and ptosis (Fig. 1, right), both patients had a surgical reduction of breast tissue. Since then, no recurrence was observed, nor was there any worsening of myasthenia.

The puberty cases concerned four young women who developed their gigantomastia at the onset of puberty, within the first months after menarche. All these young women had been initially treated for chronic arthritis, Hashimoto’s thyroiditis, psoriasis, or myasthenia associated with Graves’ disease. In all cases, the autoimmune disease was present when these young women initiated their puberty. All patients except one (i.e., patients 3, 4 and 5) were initially treated with the progestin lynestrenol (10 mg/d for 21 of 28 d) combined with the antiestrogen tamoxifen (10 mg/d), which permitted stabilization of the breast. This treatment was given until breast surgery, which involved a reduction varying from 500-4200 g per breast. After surgery, they were maintained under progestin treatment alone. Patient 6 had been treated for Graves’ disease with carbimazole, followed by total thyroidectomy when she was 10 yr old and with Ig in the context of myasthenia when she was 12 yr old. When this treatment was stopped, puberty began, together with gigantomastia, which reached a chest circumference of 125 cm (Fig. 1, middle).

Finally, patients 7 and 8 are two women who consulted at 44 and 35 yr of age. They were treated for myasthenia and chronic arthritis, respectively. No specific hormonal factor was observed. Hormonal treatments were proposed to the patients, using nonsteroid progestins but without efficacy. Patient 8 was treated with τ-penicillamine for chronic arthritis, when she developed breast gigantomastia. She was nulligest. Because τ-penicillamine has been associated with breast diseases, the treatment was stopped and changed for prednisone (45 mg/d), which permitted a stabilization of the breast volume.

Hormonal and immunological data for all those patients are presented in Tables 1 and 2.

### Hormonal measurements

Plasma concentrations of the hormones FSH, LH, prolactin (PRL) (Immunotech Beckman, Marseilles, France) and TSH (Brahms, Saint-Coulter, Hamburg, Germany), anti-double-stranded DNA antibodies were measured by RIA (Farr test) and anti-extractable nuclear antigen antibodies, by radioligand assay, using specific anti cDNA. Antithyroglobulin antibodies (Beckmann Coulter, Hamburg, Germany), antiperoxidase and anti-TSH receptor antibodies (Brahms), and anti-acetylcholine receptor antibodies were detected by RIA. Antiphospholipids (cardiolipin and β2-glycoprotein 1) were detected by ELISA. Finally, rheumatoid factor was detected by nephelometry ( latex; Dade Behring, Krefeld, Germany) and hemagglutination ( Waaler Rose; Fumouze, Levallois-Peret, France).

### Radiological investigations

All the patients had a mammogram, a breast ultrasonography, and a breast magnetic resonance imaging (MRI) examination by the same investigator. All MRI examinations were performed with a bilateral phased-array multicoil, with a 1.5-T magnet ( Signa; GEMS, Milwaukee, WI) with the patient imaged in a prone position. All examinations included sagittal T1-weighted spin-echo [500/14, repetition time (msec)/echo time (msec) and T2-weighted, fast spin-echo (4000/120) sequences, first without contrast agent. The contrast-enhanced sequence was a three-dimensional, dynamic, fast spoiled gradient-echo sequence [minimum repetition time (msec)/minimum echo time (msec), 30–90° degree flip angle, 28 sections obtained in a minimum of 90 sec, field of view (180–240 mm), large matrix (512 × 256), and thin sections (2–3 mm, with no intersection gap)] (17). Contrast material (0.1 mmol gadopentetate dimeglumine/kg body weight; Dotarem; Guerbet, Roissy, France) was injected iv for approximately 10 sec and was followed by a normal saline flush; image acquisition was begun immediately. Post-processing image subtraction was performed at a workstation with dedicated software ( Functool; GEMS).

### Histological analysis

For histological investigations, all tissue samples were routinely fixed in formalin or Bouin’s fixative and embedded in paraffin wax. Sections of 3 µm thick were stained with hematoxylin-eosin and safran.

Immunohistochemistry was performed in two cases (cases 1 and 5) on formalin-fixed material using the avidin-biotin-peroxidase complex. Antigen retrieval was performed in a water bath in citrate buffer (pH 6) for 40 min, and antibodies were incubated for 25 min. Sixteen antibodies were used for the immunohistochemical study: estradiol receptor (ER) (clone 6F11, 1:50; Novocastra, Newcastle upon Tyne, UK), progesterone receptor (PR) (clone 16, 1:200; Novocastra), anti-CD68 (clone KP1, dilution 1:200; Dako, Glostrup, Denmark), anti-CD20 (clone L26, 1:200; Dako), anti-CD3 (polyclonal, 1:250; Dako), anti-CD8 (clone 8G12/144B, 1:200; Dako), anti-CD10 (clone 56C6, 1:50; Dako), anti-CD11 (clone 2G9, 1:100; Immunotech Beckman), anti-granzyme B (clone GRB-7, 1:50; Monozan), anti-c-Kit (clone AA1, 1:400; Dako), anti-DRα (clone TAL, 1B5, 1:200; Dako), anti-smooth muscle actin (clone 1A4, 1:300; Dako), anti-
### TABLE 1. Hormonal data from the eight patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Associated disease</th>
<th>Age of onset of gigantomastia (yr)</th>
<th>Duration of symptoms (months)</th>
<th>Hormonal treatment</th>
<th>Day of cycle</th>
<th>Estradiol (25–200 pg/ml)</th>
<th>E1 (25–200 pg/ml)</th>
<th>FSH (3–12 mU/liter)</th>
<th>LH (2–5 mU/liter)</th>
<th>Testosterone (0.2–0.5 ng/ml)</th>
<th>Δ4 (0.9–1.7 ng/ml)</th>
<th>C3 (0.67–1.29 g/liter)</th>
<th>C4 (0.21–0.41 g/liter)</th>
<th>CH50 (50–150%)</th>
<th>Antinuclear antibodies</th>
<th>Immunofluorescence</th>
<th>Farr Test (N &lt; 20%)</th>
<th>Antiphospholipids antibodies</th>
<th>Anti-acetylcholine receptor antibody (&lt;1 nm)</th>
<th>TSH (0.5–3 mU/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Myasthenia</td>
<td>26</td>
<td>6</td>
<td>Progesterone</td>
<td>Under treatment</td>
<td>7670</td>
<td>NA</td>
<td>0.2</td>
<td>0.33</td>
<td>0.77</td>
<td>4.1</td>
<td>1</td>
<td>0.15</td>
<td>71%</td>
<td>1/100</td>
<td>Negative</td>
<td>Negative</td>
<td>5.3</td>
<td>9.8</td>
<td>1.8</td>
</tr>
<tr>
<td>2</td>
<td>Myasthenia</td>
<td>28</td>
<td>18</td>
<td>0</td>
<td>Pregnancy 16 wk</td>
<td>NA</td>
<td>202</td>
<td>4.7</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1/800</td>
<td>1/100</td>
<td>NA</td>
<td>Negative</td>
<td>H</td>
<td>Negative</td>
<td>8.8</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>Chronic arthritis</td>
<td>13</td>
<td>6</td>
<td>Lynestrenol</td>
<td>14</td>
<td>NA</td>
<td>NA</td>
<td>4.2</td>
<td>1.6</td>
<td>0.17</td>
<td>0.15</td>
<td>NA</td>
<td>0.15</td>
<td>80%</td>
<td>1/800</td>
<td>Negative</td>
<td>Negative</td>
<td>0.2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>Hashimoto’s thyroiditis</td>
<td>13</td>
<td>6</td>
<td>0</td>
<td>14</td>
<td>NA</td>
<td>NA</td>
<td>4.2</td>
<td>1.6</td>
<td>0.17</td>
<td>0.15</td>
<td>0.15</td>
<td>0.15</td>
<td>80%</td>
<td>1/800</td>
<td>Negative</td>
<td>Negative</td>
<td>0.2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Psoriasis</td>
<td>13</td>
<td>6</td>
<td>0</td>
<td>10</td>
<td>NA</td>
<td>NA</td>
<td>4.6</td>
<td>7</td>
<td>0.2</td>
<td>0.17</td>
<td>0.16</td>
<td>0.16</td>
<td>94%</td>
<td>1/800</td>
<td>Negative</td>
<td>Negative</td>
<td>5.2</td>
<td>1.4</td>
<td>1.2</td>
</tr>
<tr>
<td>6</td>
<td>Myasthenia, Graves’ disease</td>
<td>12</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>NA</td>
<td>NA</td>
<td>5.2</td>
<td>7</td>
<td>0.2</td>
<td>0.17</td>
<td>0.16</td>
<td>0.16</td>
<td>0.16</td>
<td>94%</td>
<td>1/800</td>
<td>Negative</td>
<td>Negative</td>
<td>2</td>
<td>1.4</td>
</tr>
<tr>
<td>7</td>
<td>Myasthenia</td>
<td>44</td>
<td>15</td>
<td>12</td>
<td>15</td>
<td>NA</td>
<td>NA</td>
<td>5.2</td>
<td>7</td>
<td>0.2</td>
<td>0.17</td>
<td>0.16</td>
<td>0.16</td>
<td>94%</td>
<td>1/800</td>
<td>Negative</td>
<td>Negative</td>
<td>2</td>
<td>1.4</td>
<td>1.2</td>
</tr>
<tr>
<td>8</td>
<td>Chronic arthritis</td>
<td>35</td>
<td>53</td>
<td>3</td>
<td>3</td>
<td>NA</td>
<td>NA</td>
<td>5.2</td>
<td>7</td>
<td>0.2</td>
<td>0.17</td>
<td>0.16</td>
<td>0.16</td>
<td>94%</td>
<td>1/800</td>
<td>Negative</td>
<td>Negative</td>
<td>2</td>
<td>1.4</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Normal ranges are shown in parentheses. NA, Not available.

### TABLE 2. Immunological data from the eight patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Associated disease</th>
<th>HLA class II</th>
<th>C3 (0.67–1.29 g/liter)</th>
<th>C4 (0.21–0.41 g/liter)</th>
<th>CH50 (50–150%)</th>
<th>Antinuclear antibodies</th>
<th>Immunofluorescence</th>
<th>Extractable nuclear antigens</th>
<th>Farr Test (N &lt; 20%)</th>
<th>Antiphospholipids antibodies</th>
<th>Anti-acetylcholine receptor antibody (&lt;1 nm)</th>
<th>TSH (0.5–3 mU/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Myasthenia</td>
<td>DRB1*03,04</td>
<td>1</td>
<td>0.15</td>
<td>71%</td>
<td>1/100</td>
<td>S</td>
<td>Negative</td>
<td>Negative</td>
<td>IgG (N &lt; 10 U)</td>
<td>5.3</td>
<td>1.8</td>
</tr>
<tr>
<td>2</td>
<td>Myasthenia</td>
<td>DRB1*01,03</td>
<td>1.15</td>
<td>0.17</td>
<td>94%</td>
<td>1/800</td>
<td>H</td>
<td>Negative</td>
<td>Negative</td>
<td>IgM (N &lt; 10 U)</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>Chronic arthritis</td>
<td>DRB1*04</td>
<td>1</td>
<td>0.17</td>
<td>80%</td>
<td>1/800</td>
<td>H</td>
<td>Negative</td>
<td>Negative</td>
<td>Anti-acetylcholine receptor antibody (&lt;1 nm)</td>
<td>5.3</td>
<td>1.8</td>
</tr>
<tr>
<td>4</td>
<td>Hashimoto’s thyroiditis</td>
<td>DRB1*07,11</td>
<td>0.75</td>
<td>0.17</td>
<td>90%</td>
<td>1/800</td>
<td>H</td>
<td>Negative</td>
<td>Negative</td>
<td>Antiphospholipids antibodies</td>
<td>Negative</td>
<td>128</td>
</tr>
<tr>
<td>5</td>
<td>Psoriasis</td>
<td>DRB1*11,13</td>
<td>1</td>
<td>0.16</td>
<td>94%</td>
<td>Negative</td>
<td>H</td>
<td>Negative</td>
<td>Negative</td>
<td>Anti-acetylcholine receptor antibody (&lt;1 nm)</td>
<td>120</td>
<td>118</td>
</tr>
<tr>
<td>6</td>
<td>Myasthenia, Graves’ disease</td>
<td>DRB1*13</td>
<td>1.23</td>
<td>0.19</td>
<td>100</td>
<td>1/400</td>
<td>S</td>
<td>Negative</td>
<td>Negative</td>
<td>Antiphospholipids antibodies</td>
<td>Negative</td>
<td>128</td>
</tr>
<tr>
<td>7</td>
<td>Myasthenia</td>
<td>DRB1*0101,08</td>
<td>1.1</td>
<td>0.19</td>
<td>80%</td>
<td>1/800</td>
<td>S</td>
<td>Negative</td>
<td>Negative</td>
<td>Anti-acetylcholine receptor antibody (&lt;1 nm)</td>
<td>100</td>
<td>108</td>
</tr>
<tr>
<td>8</td>
<td>Chronic arthritis</td>
<td>DRB1*1202,*13</td>
<td>1.2</td>
<td>0.25</td>
<td>110%</td>
<td>1/800</td>
<td>S</td>
<td>Negative</td>
<td>Negative</td>
<td>Anti-acetylcholine receptor antibody (&lt;1 nm)</td>
<td>120</td>
<td>118</td>
</tr>
</tbody>
</table>

Normal ranges are shown in parentheses. H, Homogeneous; S, speckled; C3, fraction of C3 of complement; C4, fraction of C4 of complement; CH50, total Hemolytic Complement Assay.
desmin (clone D33, 1:100; Dako), anti-CD34 (clone QBEND 10, 1:800; Immunotech Beckman), anti-vimentin (clone V9, 1:100; Dako), and anti-Ki-67 (clone MIB-1, 1:100; Dako, Glostrup, Denmark). Two samples of normal breast tissue were used as normal controls.

Indirect immunofluorescence on tissue sections

Sera were collected from patients 1, 3, 4, 5, 7, and 8 and controls. Control sera were obtained from antinuclear antibody-negative patients (n = 7) and from nine patients who had antinuclear antibodies at a detected dilution of 1:100 to 1:800. Among those nine patients, three presented with systemic lupus erythematosus and the other six patients were without overt autoimmune disease. Frozen sera were initially stored at −80°C and then thawed out and stored at 4°C. They were then applied on frozen sections of three normal breasts for 30 min at room temperature. Slides were rinsed twice in PBS. A fluorescein isothiocyanate-conjugated rabbit antihuman IgG antibody (recognizing γ-chains of human IgG) diluted at 1:40 was applied (Dako; code F0202) and incubated for 30 min at room temperature and then rinsed twice in PBS. A counterstain was made with Evans blue. In each experiment, one slide was used as negative control (no serum was applied but only PBS). Results were analyzed with a fluorescent microscope.

Results

Hormonal results (Table 1)

The patients were not all evaluated in the same conditions. Patient 1 was pregnant and patient 4 was under progestin treatment when the hormonal study was initiated. Hormonal parameters were not available in patient 2. No specific hormonal pattern was observed in the other women. With the exception of case 1 who had high estradiol levels because of pregnancy, the estradiol plasma levels ranged from 10–200 pg/ml, the latter having been measured in a patient at d 14 of a menstrual cycle. As presented in Table 1, T, Δ4, E1, progesterone, PRL, and TSH were in the normal range.

Immunological results (Table 2)

As predicted, anti-acetylcholine receptor antibodies were positive in the four patients with myasthenia, and Latex and Waaler Rose tests were positive in the two patients with chronic arthritis. Antithyroglobulin autoantibodies were detected in one patient and antiperoxidase autoantibodies in four patients. Plasma levels of the C4 fraction of complement were slightly low, averaging 0.17 g/liter (normal range, 0.21–0.41). No specific pattern of HLA haplotype was described.

Radiological investigations

Mammogram and breast ultrasonography. Breast was imaged on large films (a minimum of 24 × 30 cm) because of breast enlargement. Breast density was high and homogeneous (density 4 from BIRADS classification). Neither mass nor microcalcifications were visible (Fig. 2). Breast ultrasonography depicted hyper echoic homogeneous breast tissue, with absence of intraglandular fat of the breast.

MRI. Breast size was enlarged. Breast glandular tissue was hyperintense with T2w sequences. Peri- and intraglandular fatty tissues had disappeared as compared with normal breast. After gadolinium chelate injection, breast enhancement was diffuse and homogeneous (Fig. 3). Enhancement curves were progressive, according to normal glandular enhancement. No suspicious mass or nodule was detected on all sequences.

Pathological observations

Surgically removed breast tissues ranged from 570-4200 g (mean, 2281 g). Macroscopically, there was no focal lesion in breast parenchyma. The skin showed pseudoverrucous changes and sc edema. The adipose tissue was thin. The breast tissue was diffusely dense. Histologically, normal architecture of the breast was diffusely altered by a dense, extensive collagenous stroma, sometimes edematous, associated with an extreme rarefaction of the adipose tissue (Fig. 4A). Fibrosis was more intense

Fig. 2. Mammogram of patient 1. Note the diffuse edema and the absence of localized tumor.
in interlobular areas than in the lobules. Within the dense fibrosis, slit-like spaces were observed in the stroma, also described in pseudoangiomatous stromal hyperplasia. Lobules showed severe atrophy, and few residual glands were observed. The glandular epithelium showed some tufts. There was no hyperplasia of the myoepithelial cells. Ducts showed some cystic changes. There was a perilobular lymphocytic infiltrate made of small lymphocytes, which was more intense on biopsies performed at the beginning of the disease than on later samples (Fig. 4B).

Immunohistochemical study showed that this perilobular infiltrate was constituted of T (CD3+) lymphocytes, rarely expressing CD8 and cytotoxicity markers (TiA1 and granzyme B). CD3+ CD8+ intraepithelial lymphocytes were present and focially gathering together in the most inflammatory areas. Scattered B (CD20+) lymphocytes were observed in the interstitium, partly gathering around the vessels. B and T lymphocytes were more numerous than in normal controls. There was focal expression of major histocompatibility complex class II antigen (DRα/H9251) on glandular cells, which was not seen in normal controls. DRα was normally expressed in myoepithelial cells, similarly to control normal breast tissue. Immunohistochemical studies with anti-CD10 and anti-smooth muscle actin antibodies confirmed the absence of myoepithelial cell hyperplasia. Anti-CD34 antibody showed a somewhat denser vascular network. The cells lining the channels in pseudoangiomatous hyperplasia expressed neither CD34 nor smooth muscle actin. There was no expression of desmin, as in normal controls. There was an increase in the number of vimentin-positive fusiform cells in the fibrous stroma. Anti c-Kit antibody stained glandular cells in the lobules and sparse mast cells in the stroma, as in normal controls. Anti-Ki-67 antibody, directed against a nuclear protein expressed during cell proliferation, did not show any signal in stromal cells. Sparse epithelial cells in ducts and lobules displayed a similar Ki-67 nuclear expression both in gigantomastia and normal breast.

Staining for ER and PR was highly variable among patients. ER expression was absent in case 1 and found positive in 10–60% of epithelial cells in the other six patients studied. PR expression was also highly variable among our patients, from no staining to 90% of epithelial cells stained.

FIG. 4. A, Dense fibrosis with rarefaction of the adipose tissue and severe lobular atrophy (hematoxylin-eosin and safran; ×25); B, lymphocytic lobulitis at the early stage of the disease, with numerous intraepithelial lymphocytes (arrow) (hematoxylin-eosin, ×100); C, indirect immunofluorescence with patients' sera on normal breast tissue, showing a strong nuclear signal in lobular epithelium and cells in the stroma (×100). This signal is probably a result of antinuclear antibodies

Indirect immunofluorescence on tissue sections

Study of sera from five of six cases of gigantomastia showed a nuclear immunofluorescence pattern in normal ductal and lobular glandular epithelium and myoepithelial cells (Fig. 4C). No strong fluorescence was seen with the serum of the sixth patient (patient 5) with gigantomastia, who had no antinuclear antibodies as well as with the seven control sera without antinuclear antibodies. Nuclear fluorescence on normal breast tissue sections was observed in three of nine control antinuclear antibody-positive sera (titer ≥ 1/800; patients 14–17, Table 3). Two of them were speckled/homogeneous, and the third one was homogeneous. Results are detailed in Table 3.

Three sera of gigantomastia were also analyzed on two other normal tissues, kidney and intestine. A strong nuclear fluorescence was observed in kidney tubular and glomerular
cells as well as in epithelial and lamina propria intestine cells (data not shown).

**Discussion**

Our department has a longstanding experience in the management and follow-up of patients with benign breast diseases. In recent years, we have had the opportunity to encounter several cases of breast inflammatory hypertrophy. In all cases, these young women presented with a sudden breast gigantomastia associated with inflammatory skin signs. Even if this is a rare disorder, a most original and as-yet undescribed aspect is that, in all our patients, breast hypertrophy appeared in a context of autoimmune or immunemediated diseases, with the hormonal milieu promoting event remains highly probable. In most cases, onset of breast hypertrophy correlated with major changes in hormonal environment such as puberty or pregnancy. Among the hormones, estradiol appears as a triggering factor. First, puberty is marked by the onset of estradiol secretion, favoring the development of breast tissue, whereas pregnancy is also associated with a dramatic increase in plasma estradiol levels. Second, the observation of the stabilization of such a process under antiestrogen therapy or antigonadotropic progestins suggests that a higher sensitivity to estradiol may partly explain the breast pattern. Finally, no case has been published after menopause. However, the histological pattern described in all the cases causes us to treat this hormonal hypothesis with caution. Indeed, no epithelial proliferation was observed in our patients, even in the cases observed during pregnancy. In contrast, lobules are atrophic, and the main histological feature is a dense, diffuse fibrosis. We cannot exclude the fact that because breast biopsy has not been performed concomitantly with the onset of breast hypertrophy, the possible occurrence of transitory epithelial proliferation could not be observed, with the only available observation, a few months later, of a dense keloid scarring fibrosis. Other hormones may also be involved in this process. Because puberty and pregnancy are also associated with the appearance or the increase of secretion of progesterone and PRL, their implication cannot be excluded. Again, however, these hormones are known to exert a proliferative role on epithelial mammary cells, which was surprisingly not observed in our patients (18). Moreover, the controversial effect of bromocriptine in patients with juvenile hypertrophy may constitute an argument against the involvement of PRL in such a process (19, 20). The involvement of the hormonal milieu, even if it is not presently demonstrated, has already been suggested in various clinical breast phenotypes such as juvenile hypertrophy or gravidic hypertrophy (21–23).

The most striking feature in our group appears to be the development of such hypertrophy in a context of immunemediated diseases, with the hormonal milieu playing a promoting role. The demonstration of an immune process within the breast itself is therefore remarkable. An immune reaction was evidenced by immunohistochemical analysis of breast tissue from patients. With respect to their morphology, histological features of our cases are very close to those observed in diabetic mastopathy (10–12), myasthenia, Sjögren syndrome, systemic lupus erythematosus, or dysthyroidia (14–16, 24, 25). In these diseases, as in our patients, histological features associate T lobulocentric lymphocytic

**TABLE 3.** Results of indirect immunofluorescence study on normal breast tissue in six cases of gigantomastia and in 17 control cases

<table>
<thead>
<tr>
<th>Subject</th>
<th>Antinuclear antibodies (HEp-2 cells)</th>
<th>Clinical disease</th>
<th>Immunofluorescence pattern (normal breast)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>1 Positive 1/100 S Gigantomastia</td>
<td>Nuclear signal in ductal and lobular epithelium</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 Positive 1/800 H Gigantomastia</td>
<td>Nuclear signal in ductal and lobular epithelium</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 Positive 1/800 H Gigantomastia</td>
<td>Nuclear signal in ductal and lobular epithelium</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 Negative Gigantomastia</td>
<td>Cytoplasmic signal in the ducts</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 Positive (weak) 1/80 S Gigantomastia</td>
<td>Nuclear signal in the lobules</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 Positive 1/800 H Gigantomastia</td>
<td>Nuclear signal in ductal epithelium</td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>1 Negative No</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 Negative No</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 Negative No</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 Negative No</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 Negative No</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 Negative No</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 Negative Myasthenia gravis</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 Positive 1/200 S No</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 Positive 1/800 N No</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 Positive (weak) 1/100 S No</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11 Positive 1/100 S No</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 Positive 1/100 S No</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13 Positive 1/200 S No</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14 Positive ≥ 1/800 SH Systemic lupus erythematosus</td>
<td>Nuclear signal in ductal and lobular epithelium</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15 Positive ≥ 1/800 S Systemic lupus erythematosus</td>
<td>Nuclear signal in ductal and lobular epithelium</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16 Positive ≥ 1/800 SH Systemic lupus erythematosus</td>
<td>Nuclear signal in ductal and lobular epithelium</td>
<td></td>
</tr>
</tbody>
</table>

H, Homogeneous; N, nucleolar; S, speckled.
infiltrate. B lymphocytic vasculitis, keloid fibrosis, and progressive lobular atrophy, except that in diabetic patients, the lesions are usually focal, pseudotumoral, and without gigantomastia. Besides the histological aspect, the best argument to underline the immune reaction is the presence of myasthenia gravis in four of eight patients, more generally to underline the immune reaction is the presence of myasthenia gravis in four of eight patients, more generally of autoimmune in five of eight, the possible role of d-penicillamine in one of eight, and immune-related disease in all patients, which was unexpected considering the prevalence of these conditions in the general population. That points to a possible autoimmune background of breast gigantomastia. The absence of distortion in HLA haplotype distribution in patients is not significant providing the small number of patients studied. Moreover, the aberrant expression of HLA-DR observed in breast glandular cells has previously been reported in autoimmune diseases (16).

Results of indirect immunofluorescence confirm that nuclear signal in cases of gigantomastia was a result of the presence of antinuclear antibodies, because it was confirmed by the presence of a similar signal in intestine and kidney tissues. Even if this is a non-specific signal, this study was of interest to confirm that it is possible to detect autoantibodies on breast tissue. Furthermore, our study shows that there was no signal with the serum of patient 5, marked by the absence of antinuclear antibodies, which means that we do not detect autoantibodies reacting with breast tissue other than antinuclear antibodies. However, we obtained no direct evidence for autoimmunity in our series, because we were not able to detect organ-specific autoantibodies on breast tissue sections. That said, it should be noted that immunofluorescence was limited to the study of frozen sections that are unlikely to provide substrate for all possible autoantigens expressed by breast tissue.

The other intriguing aspect is the nearly complete absence of adipocytes in such a phenotype, replaced by an abnormal matrix accumulation. The breast MRI enabled us to observe an almost complete disappearance of the inner and peripheral fat of the breast. This feature was clearly depcted by T1w and T2w sequences. Nevertheless, MRI is not able to distinguish between mastitis and inflammatory carcinoma, and in the future, differences in dynamic enhancement might prove to be useful in follow-up of presumed mastitis. That said, the histological study clearly eliminated the possibility of a cancerous process and confirmed the absence of adipocytes.

What remains to be determined is the involvement of such a reaction in the process of gigantomastia and the relationship between the immunological factors and the hormonal factor. One hypothesis is that the preliminary immune process leads to a local inflammation, as depicted in conventional histology, followed by an abnormal matrix accumulation, as in hypertrophic keloid scars. The sudden breast development favored by hormonal events suggests that various hormonal factors may be necessary to induce this hypertrophic evolution of the immune disease.

As an alternative hypothesis, the case of patient 8 is interesting because neither puberty nor pregnancy is a decisive event in the development of gigantomastia. In her case, the d-penicillamine treatment has been associated with onset of the disease. d-Penicillamine is largely used in the treatment of chronic arthritis and has been identified as a cause of gynecomastia in men and gigantomastia in women (26, 27). This observation suggests that the hormonal milieu might not be necessarily the only promoting factor of gigantomastia.

In conclusion, we have presented eight cases of patients who, for the most part, developed in a similar clinical, radiological, and histological pattern of benign breast hypertrophy, suggesting that immune and hormonal events may be associated in this unusual disease. However, additional studies of the expression of different growth factors and/or cytokines appear to be necessary to better understand the process.

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References


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