Topics in plastic surgery of the breast
Lapid, O.

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PATHOLOGICAL FINDINGS IN GYNECOMASTIA, ANALYSIS OF 5113 BREASTS
ABSTRACT

Objective: This study aimed to analyze the histopathology results of surgically excised breast specimens with the diagnosis of gynecomastia (GM).

Summary Background Data: Gynecomastia is a term used to describe benign hypertrophy of the breast in men; it is a common, mostly transient, phenomenon in adolescents, but may also be seen in older men. Breast enlargement can lead to psychological problems; if it persists it can be surgically corrected. The obtained breast tissue specimens are routinely submitted for pathological examination. We performed this study to assess the prevalence of pathological findings after surgical management of GM.

Methods: Pathology reports were obtained from the nationwide network and registry of histopathology and cytopathology in the Netherlands (PALGA). The reports of 5113 breasts were analyzed for the prevalence of pathologies in different age groups.

Results: The average age of the patients was 35.3 ± 18.3 years (range, 1-88 years). The most common finding was GM followed by pseudo-GM. The overall prevalence of invasive carcinomas was 0.11% and of in situ carcinomas was 0.18%. The youngest patient with invasive cancer was 65 years old and the youngest patient with carcinoma in situ was 24 years old. The overall prevalence of atypical ductal hyperplasia was 0.4%; in patients younger than 20 years, it was 0.23%. The youngest patient with atypical ductal hyperplasia was 16 years old. Pathological findings were found more often in unilateral procedures.

Conclusions: The prevalence of malignancies in GM resection specimens is low; however, it increases with patient age. Unilateral cases have a statistically nonsignificant higher prevalence of pathologies.

Oren Lapid, Folkert Jolink, Sybren L. Meijer
INTRODUCTION

Gynecomastia (GM) is a term used to describe breast enlargement in men; it derives from the Greek γυνή (gyné) meaning “woman” and μαστός (mastós) meaning “breast”.

The mammary glands begin to develop in the sixth week of the fetal growth [1]. From birth until puberty the mammary glands of males and females are similar. Estrogen stimulates breast tissue development, whereas testosterone antagonizes this effect. In the peripubertal period, there is an increase in estrogen levels in boys, resulting in a transient proliferation of the ducts and the stroma. Rising androgen levels inhibit this proliferation and eventually lead to atrophy of the ducts. The normal male breast consists of a small nipple and areola, over a remnant of glandular tissue and subcutaneous fat; it is microscopically similar to the breast of prepubertal girls.

Histologically GM is a non-malignant enlargement of the rudimentary duct system; this condition consists of an unencapsulated proliferation of epithelial and mesenchymal breast components and resembles juvenile hypertrophy of the female breast.

Histologically, 3 types, or phases, of GM can be distinguished. In the florid type, an increase in the number of ducts is observed combined with proliferation of cellular, myxoid periductal stroma containing fibroblasts and myofibroblasts. Intraductal epithelial hyperplasia with recognizable papillary structures can be observed, whereas lobular changes are rare and mostly occur as a result of exogenous hormonal stimulation such as transsexual estrogen therapy. The fibrous type is seen in long-standing GM, in which the epithelial proliferation is less pronounced and a more flat epithelial lining is observed, the periductal stroma is less edematous and more hyalinized. The intermediate type with overlapping patterns of both the florid and fibrous type is also observed.

An increase in subareolar fat without enlargement of the glandular tissue, which is clinically similar to GM, is described as pseudo-GM. Duct ectasia, apocrine metaplasia, squamous epithelial metaplasia and lobular formation can occur along with GM.

Breast cancer in men is rare [2]; most are invasive ductal or unclassified carcinomas [3]. Ductal carcinoma in situ (DCIS) accounts for approximately 10% of all breast cancers in men [3]. Lobular carcinoma in situ and infiltrating lobular carcinoma of the male breast are very rare and have only been reported in case-reports [4-6].

Gynecomastia is commonly seen during different phases of life. In the neonatal period this is due to intrauterine exposure to maternal estrogen [7], and during puberty due to hormonal imbalances with a relative surplus of estrogens [8-10]. It is a common phenomenon in adolescents with an overall reported incidence between the ages of 10 to 16 as high as 48.5% [9, 11], and a peak incidence of 64.6% in the 14-14.5 year old boys [11]. In most cases GM resolves within 1 to 2 years after diagnosis. Gynecomastia is also common in the elderly due to decreased testosterone secretion and increased use of medications [12].
Different pathological etiologies have been reported, including congenital and endocrine disorders, tumors, systemic diseases, medicines, and illicit drugs. However in the majority of cases no clear etiology is found and they are identified as idiopathic.

Idiopathic adolescent GM does not require treatment, reassurance and explanation of the natural course of GM is usually sufficient as most cases regress [13]. However GM may persist and lead to the development of psychological problems [14], in such cases the treatment will be surgical removal of the surplus breast tissue. Older patients are also often operated on for GM. Most surgeons submit the resection specimens for pathological examination in order to rule out malignancy or confirm the diagnosis of GM. Missing a carcinoma or a carcinoma in situ can have serious implications for the patients, who will require further treatment; at present the survival of males with breast cancer lags behind that for females [15].

On the basis of a series of 81 patients and a literature review, Koshy et al. [16] concluded that routine pathological examination should not be performed in adolescents; however we think that a greater number of cases should be assessed before making such assertions and that the prevalence of GM should be studied in all age groups.

In this study we used data from “PALGA”, the nationwide network and registry of histopathology and cytopathology in the Netherlands [17]. We analyzed pathology reports of surgically excised breast specimens for confirmation of the clinical diagnosis of GM and the prevalence of pathologies found in the resected tissue.

METHODS

Data were obtained from the nationwide network and registry of histopathology and cytopathology in the Netherlands (PALGA) (17); the pathology results obtained by all 58 Dutch pathology departments (academic and nonacademic) are stored in this database. Retrieval is performed in accordance with the ethical guidelines of the code for proper secondary use of human tissue in the Netherlands.

All pathology results in males coded for GM were collected for a four and a half year period between January 1, 2007, and June 30, 2011. The following fields were available: an encrypted patient specific ID, age, anatomic location, the date of submission, type of procedure (fine needle aspiration, core biopsy, and excision), the conclusion of the pathology report and the specific diagnostic code.

Samples that were not obtained by a surgical excision were excluded (needle aspiration, core biopsy, and autopsy). Other interventions in our opinion erroneously coded as GM such as scar revisions or skin biopsies from the breast, were also excluded. We assessed whether the pathology results were unilateral or bilateral. When 2 unilateral specimens from the same patient were submitted on the same day the data were combined and considered to be a bilateral specimen; cases in which it
was impossible to determine if they were unilateral or bilateral were also excluded. In cases of second opinions the revised report was used.

The results reported in the conclusion of the pathology reports were classified in the following subgroups: GM, pseudo-GM, atypical ductal hyperplasia, DCIS, invasive cancer or other (benign) diagnoses.

Descriptive statistics were used to present the data as averages and prevalence. Fisher’s exact test was used to compare the groups.

RESULTS

A total of 5758 pathology reports were available for the 4.5 year period, of these 485 needle aspirations, 1038 core biopsies, 7 autopsies, 144 in our opinion erroneously coded results (see Methods section), and 111 cases in which it was impossible to define if they were unilateral or bilateral, were excluded. In 6 specimens a second opinion was requested and all revised diagnoses were similar. Four hundred ninety-six separately submitted unilateral specimens obtained from the same patient on the same day were combined into 248 bilateral results. Eighty-eight patients were operated on twice and 3 patients had 3 operations during the study period.

A total of 3719 procedures and 5113 breasts were included in the series.

The age distribution of the patients at the time of the procedures is presented in Table 1.

The average age of the patients was 35.8 ± 18.3 (range 1-88). Most interventions (n=1809, 48.5%) were performed in the age groups of 10-19 and 20-29 years, with increasing age the number of interventions decreased. The age at reoperation determined the ‘assigned age group’. The proportion of unilateral procedures increased with patient age.

Table 1. Procedure characteristics

<table>
<thead>
<tr>
<th>Age</th>
<th>Unilateral</th>
<th>Bilateral</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9</td>
<td>8</td>
<td>0</td>
<td>8</td>
<td>0.22</td>
</tr>
<tr>
<td>10-19</td>
<td>428</td>
<td>431</td>
<td>859</td>
<td>23.10</td>
</tr>
<tr>
<td>20-29</td>
<td>550</td>
<td>400</td>
<td>950</td>
<td>25.54</td>
</tr>
<tr>
<td>30-39</td>
<td>304</td>
<td>214</td>
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<td>13.93</td>
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<tr>
<td>40-49</td>
<td>308</td>
<td>147</td>
<td>455</td>
<td>12.23</td>
</tr>
<tr>
<td>50-59</td>
<td>279</td>
<td>102</td>
<td>381</td>
<td>10.24</td>
</tr>
<tr>
<td>60-69</td>
<td>263</td>
<td>68</td>
<td>331</td>
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<td>70-79</td>
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<td>5.19</td>
</tr>
<tr>
<td>80-89</td>
<td>23</td>
<td>1</td>
<td>24</td>
<td>0.65</td>
</tr>
<tr>
<td>Total</td>
<td>2325</td>
<td>1394</td>
<td>3719</td>
<td>100</td>
</tr>
</tbody>
</table>
The pathology results are summarized in Table 2 and Figure 1.

Table 2. Pathology results Specimens per breast

<table>
<thead>
<tr>
<th>Age group</th>
<th>Gynecomastia</th>
<th>Pseudo-gynecomastia</th>
<th>Atypical ductal hyperplasia</th>
<th>DCIS</th>
<th>Invasive carcinoma</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>U  B  S</td>
<td>U  B  S</td>
<td>U  B  S</td>
<td>U  B  S</td>
<td>U  B  S</td>
<td>U  B  S</td>
</tr>
<tr>
<td>0-9</td>
<td>7  0  0</td>
<td>0  0  0</td>
<td>0  0  0</td>
<td>0  0  0</td>
<td>0  0  0</td>
<td>1  0  0</td>
</tr>
<tr>
<td>10-19</td>
<td>419 814</td>
<td>6  5  32</td>
<td>5  2  0</td>
<td>0  0  0</td>
<td>0  0  0</td>
<td>2  4  1</td>
</tr>
<tr>
<td>20-29</td>
<td>538 704</td>
<td>13  6  66</td>
<td>11  1  4</td>
<td>0  0  0</td>
<td>1  0  0</td>
<td>5  0  1</td>
</tr>
<tr>
<td>30-39</td>
<td>294 366</td>
<td>7  4  44</td>
<td>5  2  0</td>
<td>2  0  0</td>
<td>0  0  0</td>
<td>2  4  0</td>
</tr>
<tr>
<td>40-49</td>
<td>295 234</td>
<td>8  9  38</td>
<td>8  1  0</td>
<td>1  0  0</td>
<td>0  0  0</td>
<td>2  6  0</td>
</tr>
<tr>
<td>50-59</td>
<td>263 152</td>
<td>6  7  36</td>
<td>5  1  2</td>
<td>1  0  0</td>
<td>0  0  0</td>
<td>8  2  0</td>
</tr>
<tr>
<td>60-69</td>
<td>245 110</td>
<td>4  8  16</td>
<td>4  2  0</td>
<td>1  0  0</td>
<td>1  0  0</td>
<td>6  2  0</td>
</tr>
<tr>
<td>70-79</td>
<td>154 56</td>
<td>2  2  2</td>
<td>1  0  0</td>
<td>1  0  0</td>
<td>2  0  0</td>
<td>3  0  0</td>
</tr>
<tr>
<td>80-89</td>
<td>21 2</td>
<td>0  0  0</td>
<td>0  0  0</td>
<td>0  0  0</td>
<td>1  0  0</td>
<td>1  0  0</td>
</tr>
<tr>
<td>Total</td>
<td>2236 2438</td>
<td>46 41 234</td>
<td>39 9 6 3</td>
<td>5 0 2</td>
<td>4 0 0</td>
<td>30 18 2</td>
</tr>
</tbody>
</table>

Figure 1. Prevalence of Invasive carcinoma and DCIS in the different age groups

The most common pathology diagnoses were GM found in 94.1% of the patients and pseudo-GM found in 5.3% of the patients. An invasive carcinoma was found in 4 patients and DCIS alone in 7.

In 2 cases the DCIS was found on one side in a bilateral procedure in a 24 and a 75 year old patient.
There were 46 bilateral pathology results with discordance between the breasts. In all such cases, one breast was diagnosed with GM and the other breast with a different diagnosis: pseudo-GM in 39, atypical ductal hyperplasia in 3, DCIS in 2 and mastopathy in 2.

In the 111 reports which were excluded because it was unclear if the operation was uni- or bilateral we found GM 94 times, pseudo-GM 16 times and granulomatous angio panniculitis once.

The overall per procedure prevalence of invasive carcinoma was 0.11% and for DCIS 0.19%. For unilateral procedures these figures are respectively 0.17% and 0.22%. For bilateral cases this figure is 0% and 0.14%. The difference in prevalence between unilateral and bilateral procedures was non-significant, for invasive carcinoma $p=0.3039$, and for DCIS $p=0.7181$. Atypical ductal hyperplasia was found in 15 patients, prevalence 0.4%, under the age of 20 the prevalence was 0.23%. The youngest patient with atypical ductal hyperplasia was 16 years old.

DISCUSSION

Gynecomastia is considered a benign finding, however despite the pre-operative workup, a malignancy or other unexpected results may be diagnosed by the pathologist after examination of the resection specimen. To determine the prevalence of such findings in patients operated on for GM we analyzed the data from a national databank of pathological reports. The advantage of using such a database is that there is no bias due to local referral patterns and that all medical centers and medical disciplines contribute to this database. This methodology also has drawbacks since we are dependent on coding by the pathologist it is therefore possible that cases of GM were not included in this database. Although national guidelines are followed it can also be expected that there are differences between pathology laboratories in the diagnostic process, for instance the number of blocks taken from a specimen and the use of ancillary techniques such as immunohistochemistry. No standardized methods were used for this retrospective study.

Another potential cause of bias is the fact that not all surgeons routinely submit all GM tissue specimens for pathological examinations, this is also often the case when GM is treated using liposuction [18], in fact guidelines have also been published that require standard examination of breast reduction specimens in women only from the age of 40 [19].

We omitted 111 reports in which it was not clear if the specimens were unilateral or bilateral, this represents 2.8% of the specimens, including these specimens in the calculations would introduce only a negligible bias, minimally reducing the prevalence of abnormal pathological findings we report in our series.

The prevalence of invasive and in situ cancer we observed is very low; these results are in concordance with the data reported by the Integral Dutch Cancer Center. For the period between 1990 and 2009, no breast malignancies were observed in males under
the age of 20 years [20]. In the group of men aged 20-29 years, 3 in situ carcinomas and 4 invasive carcinomas were reported in these 2 decades. In the years 2007 to 2011 in the Netherlands 453 invasive breast cancers were reported in males and 66,638 in females, the percentage of breast cancers in men was 0.68% of that in women [20]. For this period, invasive carcinoma detected in GM specimens represented approximately 1% of the cases of invasive cancer.

The low prevalence of invasive and in situ tumors reflects the fact that the patients were preoperatively diagnosed, treated, and operated on as GM, nevertheless there is a chance of finding a pathological finding on histopathological examination, missing a breast carcinoma can have serious implication for the patient; at present the survival of males with breast cancer lags behind that for females [15].

The overall incidence of atypical ductal hyperplasia was 0.4% with 15 cases. Two cases were seen in patients younger than 20. The clinical implications of an atypical lesion in the male breast are unclear. In the female breast atypical epithelial hyperplastic lesions are associated with an increased risk for developing breast cancer [21, 22]. This risk is raised in both breasts and does not diminish with time. If this is also applies for men; the risk of developing a malignancy is still very low. The diagnosis of atypical ductal hyperplasia is subjective to high interobserver variation [23] and it remains unclear if this should result in any change in clinical management.

CONCLUSION
The prevalence of malignancy in GM resection specimens is low however it increases with patient age. Unilateral resection specimens show a higher but statistically non-significant prevalence of malignancy.

REFERENCES
20. Nederlandse Kankerregistratie [www.cijfersoverkanker.nl/]