

A typical Ductal Hyperplasia in Gynecomastia: A Systematic Review with Case Report

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Abstract

Introduction: Gynecomastia is characterized as a benign proliferation of male breast glandular tissue as a result of hormonal imbalance. It presents as a common condition and can be present in 40% of adult men and 60% of young men. Male breast cancer is uncommon and represents less than 1% of all breast cancer. Atypical ductal hyperplasia (ADH), is a known risk factor for female breast cancer and is a rare incident in patients with gynecomastia. **Objective:** Description of a bilateral adenectomy case in a patient with gynecomastia with a finding of atypical ductal hyperplasia. **Method:** A systematic literature review and case report were conducted in the present article. **Results:** Three articles were identified that fulfilled the proposed requirements. In the present case, the decision was made to institute Tamoxifen during 5 years after bilateral adenectomy, followed by an ambulatory follow up. **Conclusion:** A lack of articles was identified concerning risks and treatment related to patients with gynecomastia and ADH. It is necessary to develop studies with adequate methodology and with more relevant case numbers. The use of tamoxifen in patients with gynecomastia and ADH seems to be the safest choice of treatment.

Keywords: Breast Cancer; Atypical Ductal Hyperplasia; Male; Gynecomastia; Tamoxifen

Introduction

Historically, the breast has been represented as a great symbol to women and society, and has been portrayed through the centuries with artistic manifestations, as in Tiepolo's art, italian artist from XVIII century, who showed the very truth of the breast, undressing it in his art "La Verità Svelata dal Tempo" (The Truth Revealed by Time).

The first stories about breasts in men appeared on 18th Egyptian dynasty, with images of the legendary Pharaoh Tutankamun and his relatives presenting gynecomastia [1].

Looking through a surgical report, the first submammary wedge resection, described as Aboul Cassis' surgery, was done by Paulus Aegineta, a Greek doctor [2].

In modern times, gynecomastia might be defined as a benign proliferation of breast glandular tissue [3], as a result of hormonal imbalance, in which there is an increase on estrogen action over androgen action in the breast tissue. It might be physiologically present in newborns due to maternal estrogenic

effect, and can be present in teenagers through a period of hormonal systemic maturation, both with spontaneous resolution. It presents as a common condition and can be present in 40% of adult men and 60% of young men [3, 4].

Other causes related to development of gynecomastia are use of medication and factors that contribute to testosterone decrease [5, 6]. In general, it is bilateral, although, it can be clinically perceived as a unilateral lesion [7].

Male breast cancer is very uncommon and represents less than 1% of all breast cancer [8]. In the same way as the female breast cancer, the major risk factors for male breast cancer are the importance of anthropometric and hormonal factors [9]. The relation between obesity and male breast cancer is notable, just as Klinefelter Syndrome (condition associated to an increase in gonadotrophins, reduced levels of androgen and normal levels of estrogens) [10] and with gynecomastia [11].

In this context, atypical ductal hyperplasia (ADH), a known finding related to higher risk of developing breast neoplasia in women, is an even rarer incident in patients with gynecomastia. So far, there is no literature consensus about best therapy after diagnosis, not even if there is an increase on the risk of breast cancer in men with gynecomastia.

Due to this scenario, a systematic literature review was necessary in order to try solving these questions and then find the best way to lead the case described below.

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Objective

Describe a case of bilateral adenectomy in a patient with gynecomastia with findings of atypical ductal hyperplasia in both surgical parts. Conduction of a systematic literature review as a scientific instrument, in order to determine therapy regarding the case.

Material and Methods

Systematic review

By selection criteria, a research was performed in the main health databases: LILACS, SciELO, PubMed/ Medline and Cochrane, during October of 2016. The "descriptors" used were atypical ductal hyperplasia e gynecomastia. The language was restricted to Portuguese, English and Spanish. Publication date was also restricted between 1990 until 2016.

No kind of restriction related to the type of study was made, due to its rarity. As inclusion criteria, articles with descriptions on ADH in male patients, without genetic syndromes, with gynecomastia diagnosis and which were available for consultation were adopted. All the articles had their title and abstracts analyzed, and those that did not correspond to the scope of the review, excluded. No statistical analyses could be done due to lack of quality data in the found articles.

The included articles in the review had their data tabulated and presented with the following terms: unilateral or bilateral gynecomastia, patient's age, medical conduct on follow up, time of follow up, neoplasia presence or not and outcome.

Case

Patient KB, male, 21 years old, born in the United States of America, no present comorbidities. His story of breast development started when he was 11 years old, achieving a volume that did not diminish in spite of physical exercise and weight loss. He denies previous treatments, traumas or other symptoms as secretion outlet or neurologic symptoms. He refers local pain in the breast region, mainly after exercises and during some days of the month. He reported embarrassment in attending beaches and locker rooms, rarely undressing himself in front of other people.

As personal antecedents, the patient denies use of illicit drugs and was a smoker (1,5 years/ packet). He reports a grandmother with breast cancer diagnosis when she was 50 years old.

During physical examination patient presents BMI of 29,95 Kg/m² and breast exam revealed bilateral gynecomastia with greater retroareolar mass on the right, classified as Simon IIb [Figure 1], with no other peculiarities.

His hormonal dosages presented no abnormalities. Breast ultrasound showed bilateral gynecomastia, without lymphadenopathy, nodules or masses.

A surgical treatment was conducted with periareolar incision and bilateral adenectomy under general anesthesia. The procedure occurred uneventfully. The parts were sent to pathological study. The patient was discharged from hospital on the same day of the surgery, with good evolution.



Figure 1: pre-operative

Results

Systematic Review

Using search criteria and descriptors on the main health database, forty-six articles were identified, which were divided in: 18: LILACS; 27: PubMed/ MedLine; 1 SciELO. No article was found on Cochrane.

After analysis, 14 articles were identified as repeatedly indexed on the databases mentioned above. Thus, the total number of articles was 31, one publication appearing repeatedly in the first three databases and 13 publications appearing in the databases LILACS and PubMed.

Circumscribing this total of articles, in analysis, only six publications remained. Following methodology mentioned above, three articles were left for analysis, two case reports and one cohort study. The data identified in the articles are arranged in the table 1.

Case

The patient evolved uneventfully. He had an excellent post-operative time, with no pain or complaints, without formation of seroma or hematomas [Figure 2].



Figure 2: 4° post-operative

Article/ Characterist	Uni or bilateral	Patient's Age	Conduct on Follow Up	Time of Follow up	Neoplasia	Outcome
Bórquez et al (2011) Atypical ductal hyperplasia in a male patient with gynecomastia: case report	Unilateral	16 years	Transareolar adenectomy was performed. There are no other procedures described.	1 year and 7 months.	No invasive ductal carcinoma was identified.	Good aesthetic result. No signs of relapse.
Wells et al (2015) Elucidating encounters of atypical ductal hyperplasia arising in gynaecomastia.	25 cases of ADH in gynecomastia were studied, in which 20% were bilateral.	Age average: 35 years old.	A cohort study, in which one third of the patients were submitted to excisional biopsy. No information about other cases.	Average; 54 months. A follow up varying from 5 months to 10 years was identified.	Presence of ductal carcinoma in situ in two cases. There is no report of invasive carcinoma.	There was no recurrence surgery for gynecomastia or development of breast cancer.
<i>Tiburzio et al</i> (2010) Bilateral atypical ductal hyperplasia, an incidental finding in gynaecomastia— Case report and literature review	Bilateral	20 years	24 months after subcutaneous mastectomy, was accomplished bilateral total mastectomy.	24 months	There was no sign of intraductal or invasive malignancy.	Residual tissue from both sides showed ADH. There is no other information about outcome.

Table 1: Abstract of analyzed articles

The result from the pathological study is as described: a product from bilateral adenectomy, right breast with a mass of 63g, left breast with a mass of 49g, both parts presented on histologic exam the presence of ducts containing homogeneous proliferation of oval cells, uniformly, with discrete alteration of the nucleus-cytoplasmic relationship, being findings consistent with atypical multifocal ductal hyperplasia.

Because of this finding, and after a systematic literature review, adjuvant treatment with tamoxifen 20mg 1x/dia during 5 years was instituted to the patient with clinical follow up that was done in the USA, his birthplace. After 12 months of follow up, there was no sign of recurrence of gynecomastia or any findings of breast cancer suspicion. The aesthetic result was adequate with great patient satisfaction [Figure 3].

Discussion

Multifocal atypical ductal hyperplasia (ADH) is characterized by a uniform proliferation of epithelial cells that are hyperchromatic, small to medium sized, rounded, cuboidal or polygonal, which remain regularly spaced, sometimes with cribriform spaces.



Figure 3: 12 months post-operative

These cells fill only part of the involved duct, in general, occupying less than 2 to 3 mm [12, 13].

Some mutations on BRCA2 germination line are findings often encountered on ADH and might encompass chromosome 1q gains, chromosome 16q losses and activation mutations in PIK3CA, gene encoding phosphoinositide 3 kinase (PIK3), components of distal pathways of growth factor receptor signaling [13].

These findings are very characteristic of individuals that develop RE-positive and Her2-negative carcinoma [13]. The onset of atypical ductal hyperplasia in men is rare, just as male breast cancer development, that can achieve 1% [14-17], resulting in death risk of 0.11%.

The presence of gynecomastia in men shows to be a risk factor for breast cancer development [9], although with uncertain increment values, with variations from 1% to 12.5% [14] of risk increase. Some publications can bring the increase up to 10 times higher [17], when compared to the risk of a person with no breast changes. However, these publications have some bias so until now there is no study with methodological quality that really defines the increased risk of breast neoplasia in men with non-syndromic gynecomastia.

In modern literature, it is possible to identify a shortage of scientific articles related to appearance of ADH in gynecomastia [18-25], a lack of consensus on the determination of ADH as a risk factor to development of male breast cancer, and also anything related to therapy to be adopted after diagnosis.

An already well-established fact in women, HDA has been associated with an up to 4 time increase in the risk of developing breast cancer compared to women without such transformations [26]. As a medical conduct, for use in the female population, there is a large literature demonstrating consensus in indicating the use of tamoxifen 20mg 1x/day during 5 yrs, with the aim of reducing the risks of developing of breast cancer, achieving reductions of up to 48% [27, 28].

Genetic mutation studies of BRCA 1 and 2 genes as risk predictors for the development of breast and ovarian neoplasia have been widely used, mainly associated to familiar cancer cases [29,30]. Several studies have been accomplished to clarify the role of these mutations in male breast cancer, however these are still inconclusive studies, without strong bases to change medical conducts. A Italian multicentric study [31,32] showed a relation of BRCA 2 with the development of a more aggressive type of male breast cancer, with specific expression in the male sex, but there are no studies regarding patients with gynecomastia and diagnosis of ADH that allow us to connect these same alterations with the development of breast cancer in men.

So it is possible that tracking back a mutation on BRCA 1 and 2 genes in patients with gynecomastia, and association with the diagnosis of ADH, brings a possible benefit as a way of tracking patients with a higher risk of developing breast cancer, as it has already been demonstrated in female patients.

We have learned from the systematic review carried out, that the majority, and maybe all of the articles are represented as cases reports, studies of very little scientific quality and that do not represent any advance to medical knowledge, but which portray how rare the finding of atypical multifocal ductal hyperplasia is in gynecomastia patients. In the review above mentioned, we have found three studies which framed a situation that may give us indications of a higher incidence of neoplasia in patients with gynecomastia and ADH.

Wells et al. [21] demonstrated that among 25 cases of ADH in patients with gynecomastia, two cases were found of ductal carcinoma in situ, which would correspond to an incidence of 8% in this specific sample, with a higher value than those determined in the literature for

patients with gynecomastia. This observation, despite lacking strong scientific evidence due to low methodological quality and small number of cases studied, it guided the therapy adopted in the patient of the present report.

The other articles included in the systematic review demonstrated a certain safety in only performing the surgical treatment and clinical follow-up, but this was short term, which does not ratify this supposed safety.

As previously mentioned, there is a 4-fold increase in the risk of developing neoplasia in female patients diagnosed with ADH [26], and for them, literature shows a benefit in using tamoxifen [27, 28]. Therefore, due to this drug being included among therapeutic arsenal to gynecomastia and having few side effects, it was decided, after bilateral adenectomy for the treatment of gynecomastia, to prescribe 20mg once a day for the period of five years, using the same protocol of the female patients, in addition to clinical follow-up.

Conclusion

The systematic literature review framed the lack of studies related to the risks and medical conducts to be taken in patients with gynecomastia and ADH. Such shortages concern both number and quality of the papers presented, and do not provide enough evidence for a consensus of treatment, screening and prevention in the patients with gynecomastia.

According to the review in patients with gynecomastia and ADH, there are indications of an increased risk of developing breast neoplasia, and that the treatment for this, generates little or no side effect. Therefore, it can be established that with the current knowledge, when weighing risk-benefit, there is a clear indication towards the use of tamoxifen as adjuvant in the treatment of the patients with gynecomastia and ADH, that might result in a reduction on neoplasia rates.

Such considerations must be ratified by conducting studies with adequate methodological quality and with relevant number of cases, as already portrayed in the tangent to female patients.

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