REVIEW

Is routine pathological evaluation of tissue from gynecomastia necessary? A 15-year retrospective pathological and literature review

Jenna-Lynn Senger MD[1], Geethan Chandran MD FRCSC[2], Rani Kanthan MBBS MS FRCS FRCPC MEd[3]

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OBJECTIVE: To reconsider the routine plastic surgical practice of requesting histopathological evaluation of tissue from gynecomastia.
METHOD: The present study was a retrospective histopathological review (15-year period [1996 to 2012]) involving gynecomastia tissue samples received at the pathology laboratory in the Saskatoon Health Region (Saskatchewan). The Laboratory Information System (LIS) identified all specimens using the key search words "gynecomastia", "gynaecomastia", "gynecomazia" and "gynaecomazia". A literature review to identify all cases of incidentally discovered malignancies in gynecomastia tissue specimens over a 15-year period (1996 to present) was undertaken.
RESULTS: The 15-year LIS search detected a total of 452 patients that included two cases of pseudogynecomastia (0.4%). Patients' age ranged from five to 92 years and 43% of the cases were bilateral (28% left sided, 29% right sided). The weight of the specimens received ranged from 0.2 g to 1147.2 g. All cases showed no significant histopathological concerns. The number of tissue blocks sampled ranged from one to 42, averaging four blocks/case (approximately $105/case), resulting in a cost of approximately $3,200/year, with a 15-year expenditure of approximately $48,000. The literature review identified a total of 15 incidental findings: ductal carcinoma in situ (12 cases), atypical ductal hyperplasia (two cases) and infiltrating ductal carcinoma (one case).
CONCLUSIONS: In the context of evidence-based literature, and because no significant pathological findings were detected in this particular cohort of 452 cases with 2178 slides, the authors believe it is time to re-evaluate whether routine histopathological examination of tissue from gynecomastia remains necessary. The current climate of health care budget fiscal restraints warrants reassessment of the current policies and practices of sending tissue samples of gynecomastia incurring negative productivity costs on routine histopathological examination.

Key Words: *Best practice guidelines; Gynecomastia; Histopathology; Male breast cancer; Risk factors for male breast cancer*

L'évaluation pathologique systématique des tissus de gynécomastie est-elle nécessaire? Une étude pathologique rétrospective sur 15 ans et une analyse bibliographique

OBJECTIF : Revoir la pratique chirurgicale systématique qui consiste à demander une évaluation histopathologique des tissus de gynécomastie.
MÉTHODOLOGIE : La présente analyse histopathologique rétrospective (sur 15 ans [1996 à 2012]) portait sur les prélèvements de tissus de gynécomastie reçus au laboratoire de pathologie de la Régie régionale de la santé de Saskatoon, en Saskatchewan. Le Système d'information de laboratoire (SIL) a répertorié tous les prélèvements au moyen des mots-clés *gynecomastia*, *gynaecomastia*, *gynecomazia* et *gynaecomazia*. Une analyse bibliographique a permis de repérer tous les cas de cancers découverts fortuitement dans des prélèvements de tissu de gynécomastie sur une période de 15 ans (1996 à maintenant).
RÉSULTATS : La recherche du SIL sur 15 ans a décelé un total de 452 patients, dont deux cas de pseudogynécomastie (0,4 %). Les patients avaient de cinq à 92 ans, et 43 % des cas étaient bilatéraux (28 % du côté gauche, 29 % du côté droit). Le poids des prélèvements reçus variait entre 0,2 g et 1 147,2 g. Aucun cas ne suscitait de préoccupations histopathologiques. De un à 42 blocs de tissu avaient été prélevés, pour une moyenne de quatre blocs par cas (environ 105 $ par cas) et un coût d'environ 3 200 $ par année, ce qui correspond à des dépenses d'environ 48 000 $ sur 15 ans. L'analyse bibliographique a permis de repérer un total de 15 observations fortuites : carcinome canalaire *in situ* (12 cas), hyperplasie canalaire atypique (deux cas) et carcinome canalaire infiltrant (un cas).
CONCLUSIONS : Compte tenu des publications fondées sur des données probantes et de l'absence d'observations pathologiques significatives au sein de cette cohorte de 452 cas associés à 2 178 lames, les auteurs pensent qu'il est temps de réévaluer la nécessité des examens histopathologiques systématiques des tissus de gynécomastie. Dans le climat actuel de compressions budgétaires dans le domaine de la santé, il est justifié de réévaluer les politiques et pratiques actuelles consistant à envoyer des échantillons de tissus de gynécomastie qui nuisent aux coûts de productivité de l'examen histopathologique systématique.

Gynecomastia, from the Greek gyne (female) + mastos (breast), is a condition characterized by an increase in the ductal tissue, stroma and/or fat of the male breast resulting in male breast enlargement. Ducts of the breast demonstrate variable degrees of multiplication, elongation or branching within the background of an infiltrate of inflammatory cells (1). On histopathological examination, three types of gynecomastia have been described (2). Type 1 (florid type) is characterized by a large number of ducts with irregular lumens and three or more epithelial layers surrounded by loose connective tissue that is well demarcated from the surrounding stroma. This type is most common in immature 'young' gynecomastia of <4 months duration. Type 2 (fibrous type), by contrast, exhibits only a slight increase in the number of ducts with greater stromal fibrosis, and is most common in mature 'older' gynecomastia of >1 years' duration. Type 3 (intermediate type) appears between four and 12 months, and is believed to represent the transition from florid to fibrous tissue.

Gynecomastia is believed to result from an imbalance in the estrogen to androgen ratio, causing proliferation of breast tissue cellular components. As such, this condition has a predominantly trimodal peak of age distribution, correlating to times of higher levels of estrogen, comprising the neonatal, adolescent (prepubertal, pubertal) and elderly populations (3,4). Adult gynecomastia is rare and usually requires further evaluation for an underlying secondary cause. In each of these populations, the gynecomastia can present either unilaterally or bilaterally. Unilateral gynecomastia in all age populations requires an increased investigational work-up compared with men with bilateral presentations because unilateral resection specimens may show a higher, but statistically nonsignificant, prevalence of malignancy (5). The majority of gynecomastias are idiopathic in nature; secondary causes include hypogonadism (trauma, castration, orchitis, Kleinfelter syndrome), endocrine disorders (hyperthyroidism), metabolic disorders (cirrhosis), neoplasms (testicular, adrenal, bronchogenic

[1]*College of Medicine;* [2]*Department of Plastic Surgery, University of Saskatchewan;* [3]*Department of Pathology & Laboratory Medicine, Royal University Hospital, Saskatoon, Saskatchewan*
Correspondence: Dr Rani Kanthan, Room 2868, 'G-Wing', Department of Pathology & Laboratory Medicine, Royal University Hospital, 103 Hospital Drive, Saskatoon Saskatchewan S7N 0W8. Telephone 306-655-2158, e-mail rani.kanthan@saskatoonhealthregion.ca

carcinoma) or pharmacological agents (including cimetidine, digitalis, methadone, marijuana, clomiphene, chemotherapeutics/hormonal therapy, antiretrovitals, chlorpromazine and anabolic steroids) (3,6-8).

Neonates and pubertal patients often require reassurance and 'benign neglect' for at least one year because the excess breast tissue often recedes with time. While several classification systems have been proposed to stratify the severity of gynecomastia, including that of Simon et al (9), McKinney and Lewis (10), and Rohrich et al (11), the American Society of Plastic Surgeons classifies male breast enlargement into four grades based on clinical appearance (8):

- Grade I: small breast enlargement with a localized collection of peri-areolar tissue.
- Grade II: moderate breast enlargement exceeding areolar boundaries, with indistinct borders from the chest.
- Grade III: moderate breast enlargement exceeding areolar boundaries, with distinct borders from the chest and associated with excess skin.
- Grade IV: marked breast enlargement and feminization associated with excess skin.

Although breast size in most patients spontaneously regresses and, thus, observation is an appropriate form of management, more aggressive therapy may be required in a subset of patients with persistent enlargement.

Patients with grade II to IV gynecomastia are potential surgical candidates, with options including subcutaneous mastectomy, liposuction with or without ultrasound guidance, or a combination of both techniques. The number of patients undergoing surgical treatment for gynecomastia shows an increasing trend (12).

Current practices in Canada mandate that gynecomastia specimens undergo histopathological evaluation to obtain a definitive tissue diagnosis. It is likely that this practice stems from a historical tradition rather than evidence-based guidelines. In the current era of increasing health care expenses, it is time to re-evaluate the necessity of the continued practice of routine histopathological evaluation of gynecomastia tissue specimens. This hypothesis was examined in the present study. The purpose of the present study was twofold: to assess the results of current routine histopathological evaluation of gynecomastia tissue specimens; and to review the current literature for contextual evidence-based guidelines.

METHODS

A retrospective 15-year (1996 to 2012) surgical pathology review of all gynecomastia tissue samples within the Saskatoon Health Region (Saskatchewan) was conducted, with identification of the cases in the Laboratory Information System (LIS) using the key words "gynecomastia", "gynaecomastia", "gynecomazia" and/or "gynaecomazia". The pathological reports were reviewed for demographics and final diagnosis. All slides underwent histopathological evaluation to confirm the diagnosis.

In addition, a 15-year (2002 to 2013) systematic literature review using PubMed and Medline was performed. Search terms including "gynecomastia" with ("breast neoplasm" OR "carcinoma" OR "hyperplasia") generated a list of approximately 600 articles. These were analyzed for content relevance and secondary references were identified using the PubMed 'Related Articles' feature, with the focus being the presence of primary premalignant or malignant breast neoplasms discovered incidentally in the treatment of gynecomastia. The search was limited to English-language articles.

RESULTS

A total of 452 patients were identified in the retrospective review, comprising 2178 slides. Patients' age ranged from five to 92 years (median 31 years). The majority of patients were 11 to 20 years of age, following which the incidence progressively decreased with a second peak in patients >70 years of age (Figure 1). The majority of cases were bilateral (43%) and, among unilateral cases of gynecomastia, the incidence of right-sided gynecomastia (29%) was comparable with left-sided (28%).

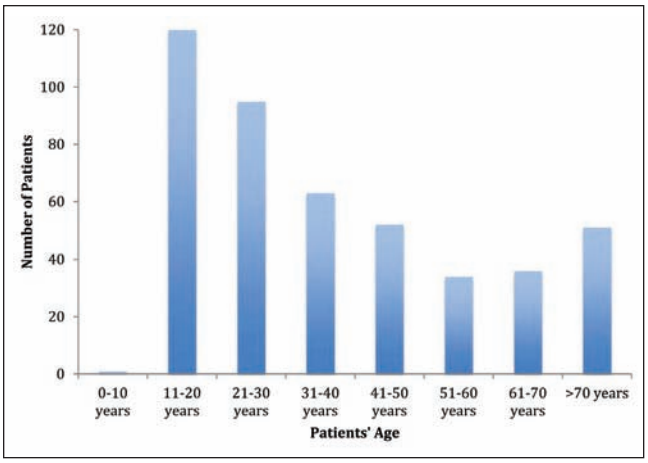

Figure 1) *Histogram illustrating the age distribution of the patients identified in the 15-year retrospective review. The y-axis indicates the number of patients per category; the x-axis indicates the eight age categories, spanning from 0 to >70 years in 10-year increments. The majority of patients were 11 to 20 years of age. The incidence of patients >20 years of age decreased with increasing age; however, a second peak after 70 years of age was observed*

Pathological review

Gynecomastia was confirmed in 99.6% while 0.4% of cases were pseudogynecomastia (mature adipose tissue only – no breast). No premalignant or malignant lesions were identified in any of the reviewed cases. On gross examination, specimen weights ranged from 0.2 g to 1147.2 g, averaging 79 g/specimen. Consistent with this wide weight range, the number of blocks (tissue section for microscopic evaluation) taken varied from one to 42, with a mean of four blocks/case. The average cost to process and read slides in Saskatoon is approximately $105/case; therefore, analysis of gynecomastia specimens incurs a yearly expenditure of approximately $3,200. This is equivalent to approximately $48,000 to achieve these negative results over the 15 years covered in the present study.

Literature review

The literature review from 1996 to present identified 15 case studies investigating an incidentally discovered invasive or in situ lesion in gynecomastia tissue specimens obtained at surgery. These results include patients of all ages who underwent surgical treatment for gynecomastia and were found to have a malignancy incidentally. Patients' ages ranged from 15 to 70 years (mean 26 years) and were detected bilaterally in eight cases, and isolated to the right breast in three cases and to the left breast in two cases. The most common diagnosis reported was ductal carcinoma in situ (DCIS), detected in 12 patients, and atypical ductal hyperplasia (ADH) in two patients, as summarized chronologically in Table 1 (1,3,6,7,13-21). Obesity was reported in three cases (12,15,19). Serum karyotyping for Kleinfelter syndrome was reported negative postoperatively in six cases (3,12,14,15,18,20). *BRCA* mutations were reported negative in the three analyzed patients (12,15,17). However, it should be emphasized that these cases represent a select population of incidentally discovered male breast malignancy in routine histopathological examination of gynecomastia tissue samples; thus, they were not expected to present with any of the well-known risk factors for male breast cancer (MBC).

The outcomes for these positive breast cancer diagnoses (DCIS and ADH) in incidentally discovered gynecomastia included total bilateral mastectomy with or without nipple-areolar-complex reconstruction in the majority (n=10) of cases. The remaining four cases did not report any further surgical management and were followed-up with regular clinical examinations.

TABLE 1
Literature review* (1996 to present) of incidentally discovered breast (pre)malignancy in gynecomastia tissue

Author (reference), year	Age, years	Presentation	Surgical technique	Laterality	Histopathology
McCoubrey et al (13), 2011	17	Unilateral swelling breast	Nipple-sparing mastectomy	Left	Ductal carcinoma in situ
Gunaydin and Altundag (14), 2011	23	Bilateral gynecomastia	Bialteral subcutaneous mastectomy with NAC grafting	Right	Ductal carcinoma in situ
Lemoine et al (15), 2011	15	Bilateral gynecomastia	Subcutaneous mastectomy	Bilateral	Ductal carcinoma in situ
Noor et al (16), 2011	54	Bilateral gynecomastia, painful	Liposuction followed by subcutaneous mastectomy	Bilateral	Ductal carcinoma in situ
Coroneos and Hamm (17), 2010	25	Periareolar discomfort, swelling, gynecomastia	Subcutaneous mastectomy	Left	Ductal carcinoma in situ
Chang et al (3), 2008	16	Unilateral gynecomastia	Subcutaneous mastectomy and contouring liposuction	Left	Ductal carcinoma in situ
Corroppolo et al (18), 2008	15	Bilateral gynecomastia	Bilateral exeresis of mammary gland	Right	Ductal carcinoma in situ
Qureshi et al (19), 2007	26	Bilateral gynecomastia, subareolar disc of tissue palpable	Staged subcutaneous mastectomy	Bilateral	Ductal carcinoma in situ
Liao et al (12), 2007	24	Gynecomastia obesity, breast ptosis	En bloc total excision with NAC grafting	Bilateral	Ductal carcinoma in situ
Staerkle et al (7), 2006	30	Gynecomastia, subareolar mass bilaterally	Subcutaneous bilateral mastectomy	Bilateral	Ductal carcinoma in situ
Wadie et al (20), 2005	16	Gynecomastia, subareolar disc of tissue bilaterally	Subcutaneous mastectomy	Right	Ductal carcinoma in situ
Hamady et al (1), 2005	24	Gynecomastia pain, tenderness	Subcutaneous mastectomy	Bilateral	Atypical ductal hyperplasia
Prasad et al (6), 2005	20	Gynecomastia	Subcutaneous mastectomy	Bilateral	Atypical ductal hyperplasia
Wilson et al (21), 2004	18	Gynecomastia neurofibromatosis-1	"Bilateral breast reduction"	Bilateral	Ductal carcinoma in situ

**Identified using PubMed and MedLine, as reported in the English language. NAC Nipple aerolar complex*

DISCUSSION

MBC is a rare neoplastic process, accounting for only 0.17% of male neoplasms and <0.1% of overall cancer-related mortality in men, occurring at a mean age of 60 years (12,22,23). The precise carcinogenesis of MBC remains poorly understood, with current understandings of female breast cancer pathogenesis being nontransferable to the understanding of the development of the male counterpart (23,24,25). Identified risk factors for the development of this rare condition can be broadly divided into four categories (26,27), which are summarized in Table 2.

A. **Genetic events** that predispose to the development of MBC include Klinefelter syndrome, *BRCA* -1/-2 mutations, and a first-degree relative with either female or MBC. Patients with Klinefelter syndrome have a 20× to 50× increased risk for developing MBC (28). Other germ-line mutations, such as PALB2, androgen receptor, CYP17 and CHEK2, may play a role in the development of MBC; however, insufficient data are available to support or refute these conclusions.

B. **Endocrine risk factors** that have been identified include obesity, use of exogenous estrogen and/or testosterone, orchitis and epididymitis, all of which increase the relative amount of estrogen levels relative to androgen. Within the peripheral adipose tissue, androgens are aromatized to estradiole and androstenedione to estrone; therefore, obese males have increased estrogen levels. In contrast, the hypoestrogenic effects of cigarette smoking may be protective against MBC (22,28).

C. **Environmental exposure** to radiation, high temperatures (occupational) or electromagnetic fields has been attributed to a higher breast cancer risk in men.

D. **Sociodemographic factors** may additionally contribute to the development of MBC. It is well established that the incidence of MBC increases with age, generally occurring five to 10 years later in life than breast cancer in females (26). Additional sociodemographic risk factors, including African or Ashkenazi Jewish ancestry, and a sedentary lifestyle, never married or excessive alcohol consumption have also been reported in association with MBC in the published literature. Possible miscellaneous risk factors reported include possible higher risk in first borns and an association with bone fracture after 45 years of age (26).

In men, cancerous lesions usually present as a painless hard subareolar lump in the seventh to eighth decade of life (23,26). The presence of a palpable lump, particularly if well demarcated from the surrounding breast tissue, should raise concerns of a possible underlying malignant process. Additional clinical features that may indicate a pathological process include nipple changes including retraction or bloody discharge. Skin changes, such as dimpling, puckering, redness, scaling or *peau d'orange*, warrant further investigation.

DCIS in males is an extremely rare finding. The diagnosis of 'male DCIS', therefore, remains debatable. In females, DCIS is believed to arise from the terminal ductal lobular unit; however, the male breast does not contain terminal ductal lobular units, thus challenging the very existence of these 'DCIS' lesions as reported in the literature. However, some authors believe that DCIS in males may arise from the epithelium of larger ducts (7). In men, 'DCIS' most often presents as a unilateral subareolar mass in the presence of nipple discharge at a median age of 65 years (3). Many of these are associated with an infiltrating tumour, with only 5% of cases being isolated DCIS (3,13). Risk factors include hyperprolactinemia and exogenous estrogens (7). No consensus guidelines exist for the management of this patient population (13). Axillary lymph node dissection is not performed in these patients, and treatment options include lumpectomy, local excision with radiotherapy or mastectomy (20). The risk of malignant transformation in men with ADH remains even more poorly understood (6). ADH has been reported to occur in <2.5% of adolescent gynecomastia; however, the existence and significance of this finding remains unclear (4).

Historically, some have assumed that gynecomastia conferred an increased risk of developing breast cancer; however, research investigating this question has clearly demonstrated otherwise. A prospective cohort study by Olsson et al (29) followed 446 patients with gynaecomastia over a 30-year period and found no occurrences of MBC, although a significant increased risk of testicular cancer, squamous cell carcinoma of the skin and esophageal cancer was observed.This allows

TABLE 2
Male breast cancer risk factors

Category	Risk factor
Genetic	Family history in first-degree relative (male or female)*
	Klinefelter syndrome*
	BRCA-1 or *BRCA-2* mutation*
Endocrine (altered androgen:estrogen ratio)	Obesity
	Exogenous estrogen/testosterone use
	Orchitis
	Epididymitis
Environmental exposure to:	Radiation
	High temperature (occupational)
	Electromagnetic fields
	Volatile organic compounds (tetrachloroethylene, perchloroethylene, tricholorthylene, dicholorthylene, benzene chemicals)
	Finasteride
Sociodemographic	Ashkenazi Jewish
	African ancestry
	Sedentary lifestyle
	Single marital status
	Heavy alcohol use

**Indicates a 'major risk factor', all additional factors are 'minor risk factors'*

us to conclude that men with gynecomastia have the same risk of developing breast cancer as men who do not have this condition. MBC accounts for <1% of all breast neoplasms; therefore, the likelihood of discovering a malignancy in mastectomy specimens from gynecomastia patients is approximately 100-fold less likely than incidentally finding breast cancer in tissue removed from a female who undergoes a reduction mammoplasty. Because the incidence of occult breast cancer identification in female reduction mammoplasty specimens is 0.06% to 1.2%, the likelihood of detecting MBC in gynecomastia tissue samples is extremely low (0.0006% to 0.012%) (12).

This quantitative low risk of malignancy in gynecomastia tissue is further reflected in the literature by case studies and case series. A recent study involving 5113 breasts with gynecomastia conducted by Lapid et al (5) found prevalence rates of 0.11% of invasive cancer and a 0.18% of in situ malignancy. Malignancies in this study were, however, not limited to incidental findings. Additionally, a study by Kasielska and Antoszewski (30) reviewed 113 gynecomastia patients and found no malignancies. Similarly, in 81 patients reviewed by Koshy et al (4), there was one patient with cellular atypia, but no malignancies were detected. These same authors conducted a literature review of pathologies found in gynecomastia tissue of adolescents (<21 years of age), either found incidentally or under suspicion, over the past 45 years. In this review, they found only six reports of cancer and five cases of atypical ductal hyperplasia. These reviews are consistent with the findings of our literature review, which identified only 15 cases of incidentally detected premalignant/malignant lesions in gynecomastia tissue, emphasizing the extreme rarity of such lesions.

Furthermore, it is increasingly well recognized that a substantial portion of the health care budget, an estimated $700 billion annually in the United States, is spent on "needless or low-benefit procedures" (31). Despite this understanding, few guidelines have been created to minimize such spending. Strategies that challenge the status quo and set a new precedent for budget-conscious health care delivery are, thus, required. In this context, we propose guidelines for the best-practice management of gynecomastia that are both evidence and consensus based, which we hope will provide an impetus to review and change current policies and existing practices.

We propose that not all tissue samples obtained by mastectomy for gynecomastia necessitate histopathological evaluation. The decision to proceed to histopathological evaluation is multifactorial and should include major and minor risk factor assessments based on both clinical

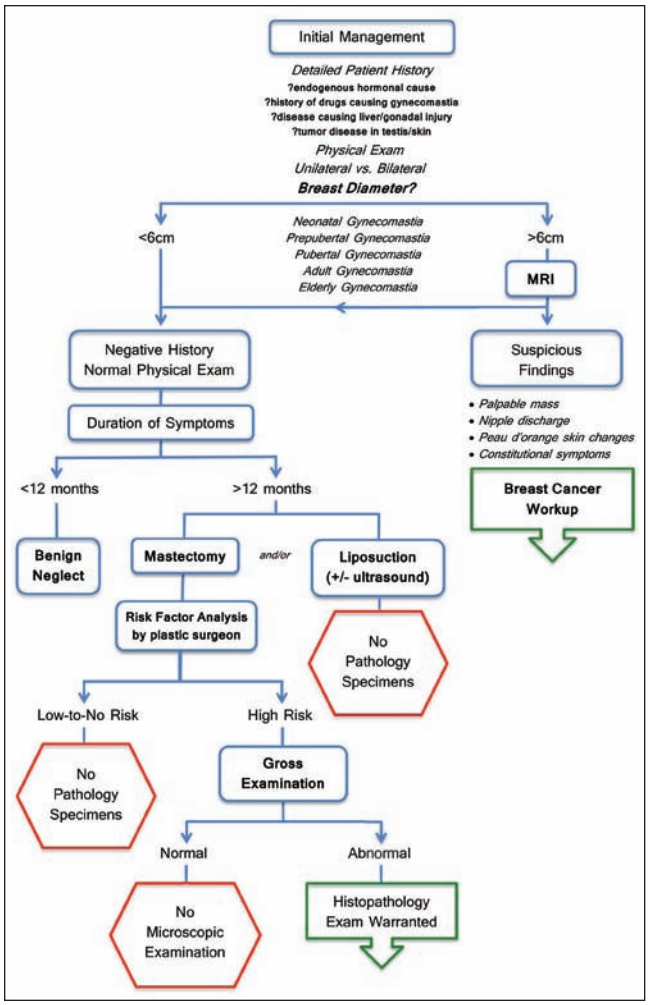

Figure 2) *Flow-chart outlining the authors'suggested best practice guidelines for the management of gynecomastia tissue samples, which includes an initial detailed history/physical examination (Exam). It is recommended that all breasts with diameters >6 cm undergo screening magnetic resonance imaging (MRI). Any features suspicious for male breast cancer should prompt a complete breast cancer workup. Otherwise, patients symptomatic for >12 months may be treated. An evaluation of risk factor assessment by the plastic surgeon (see Table 2) will determine whether tissue specimens should be sent for histopathological examination*

and intraoperative findings by the plastic surgeon. Examples of such risk factors may include evidence of Klinefelter syndrome, or features on history or physical examination suggesting a pathological process such as an acute onset with rapid progression, a palpable irregular mass, or bloody nipple discharge or other clinical presentations that have been reported to be associated with malignant or premalignant lesions such as retroareolar pain and swelling (32). Given the rarity, guidelines for screening of MBC by mammogram and/or magnetic resonance imaging are ill-defined; however, Qureshi et al (19) suggest that in the preoperative planning of gynecomastia surgery for breast diameters >6 cm, magnetic resonance imaging to exclude the presence of malignancy is, perhaps, warranted (19). In the absence of risk factors, pathological evaluation of tissue samples from gynecomastia should occur at the discretion of the plastic surgeon. Recommendations to proceed to pathological evaluation are, thus, twofold: first, we suggest that in patients with increased risk factors for MBC, tissue samples obtained at mastectomy should be sent to the pathology laboratory for gross examination. The presence of any visible or palpable pathology will then mandate a microscopic examination. In the absence of any

lesion detected at gross examination, no further sections are recommended. Figure 2 summarizes a proposed evidence-based guideline for the management of tissue samples of gynecomastia.

CONCLUSIONS

The gynecomastia population is not at an increased risk for developing breast cancer. Because their risk (0.17%) is identical to the remainder of the male population, we recommend a change in the current practice of routine histopathological evaluation of gynecomastia tissue specimens. In congruence with the literature, we found no pathology in the 452 patients of gynecomastia treated in Saskatoon over the past 15 years; however, evaluation of these cases cost the Saskatoon Health Region approximately $48,000. A review of the literature supports the rarity of incidentally discovered malignancies in gynecomastia specimens, indicating this is a highly uncommon occurrence. With the rising cost of health care, we suggest a stratified approach to the management of gynecomastia. Guidelines, as suggested in our recommendation, are a feasible option to assure that funding is directed toward alternative high-yield cancer prevention and treatment strategies.

DISCLOSURES: The authors do not have any financial disclosures or conflicts of interest to declare.

ETHICS APPROVAL: Because all relevant patient material in this case report was completely de-identified, it was considered exempt from formal ethics approval from the institutional review board.

DISCLAIMER: This study was presented, in part, as an oral presentation at the Canadian Society of Plastic Surgeons Annual Meeting (CSPS) in Calgary, Alberta, May 28 to June 1, 2013.

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