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**Abstract**

Aims:

Gender dysphoria is a diagnosis wherein an individual identifies as the opposite gender. Management of patients seeking female-to-male (FTM) transition includes hormonal therapy and surgical intervention, including mastectomy. We aim to characterize the immunohistologic findings in resection specimens from FTM patients.

Methods and results:

We reviewed 68 cases (67 patients, 1 with re-excision) of FTM breast tissue resection by collecting clinical data, reviewing breast imaging and pathology reports (gross fibrous density, specimen weight and number of cassettes submitted), and reviewing pathology slides (number of tissue pieces submitted, number of terminal duct lobule units [TDLUs], and presence of histologic findings).

Significant histologic findings were present in 51/68 (75.0%) cases and included one case (1.5%) of flat epithelial atypia. Fibrocystic changes were the most common finding (27/68, 39.7%), followed by gynecomastoid change, fibrotic stage, (22/68, 32.4%) and fibroadenomatoid change (11/68, 16.2%). Fibrocystic change was associated with increased TDLUs and gynecomastoid change was associated with lower body mass index and decreased TDLUs. Gynecomastoid change showed a moderate proportion of luminal epithelial cells with strong intensity staining via estrogen receptor, progesterone receptor and androgen receptor immunohistochemistry and a 3-layered epithelium via cytokeratin 5/6 immunohistochemistry.

Conclusions:

We identified gynecomastoid change at a significantly higher rate than previously reported in female patients. We support the continued gross and histologic evaluation of FTM specimens in light of identification of atypia in one case.

**Key words**: breast, pathology, transgender, gender dysphoria

**Abstract word count:** 227

**Introduction**

Gender dysphoria is a diagnosis wherein an individual's gender identity differs from external sexual anatomy at birth.[1] The true incidence of gender dysphoria remains uncertain. Previous estimates of prevalence were based on indirect calculations of those who apply for gender reassignment, receive a diagnosis of gender dysphoria, start gender-affirmation treatment and/or apply for legal gender recognition.[2-10] By recent population-based survey methods, 0.6% of adults (1.4 million individuals) and 0.7% of youth age 13-17 (150,000 individuals) in the United States identify as transgender.[11-12] Management of patients seeking female to male (FTM) transition includes hormonal therapy and surgical intervention.[13-14] As patients are increasingly seeking gender-affirming surgery, Michigan Medicine has become a destination center for patients seeking surgical intervention for gender dysphoria.[2]

Currently, there is limited data in the published literature on the histologic findings from resection specimens from FTM gender-affirming surgeries. The most commonly-reported changes are fibrosis, atrophy and fibrocystic changes.[15] Here we aim to provide a comprehensive review of the clinical characteristics, gross findings and immunohistologic features in FTM breast specimens.

**Materials and Methods**

Case Selection

Following institutional review board approval, all cases of FTM transgender-affirmation with resection of breast tissue (1998-2016) were retrieved from Michigan Medicine Department of Pathology archives.

Clinical and Pathologic Data

Clinical data, including patient age, body mass index (BMI), presence and duration of hormone therapy, smoking history, parity, breast imaging findings, and family history were retrieved from medical records. Specimens had previously undergone gross and histologic evaluation via standard protocol. All patient pathology reports and slides were available for review. Pathology reports were reviewed for weight, gross fibrous density (% fibrous tissue), the presence of gross lesions, number of tissue pieces submitted for microscopic examination, and the number of cassettes submitted per case. All hematoxylin and eosin (H&E) slides were reviewed by two pathologists (EGE, JMJ) for the number of terminal duct lobular units (TDLUs) per case and the presence of histologic findings. TDLUs were scored as absent if none were present, rare if 1-3 were present, and frequent if greater than 3 were present.

Immunohistochemistry

Immunohistochemical (IHC) stains were performed on 22 cases with gynecomastoid change. Commercially-available antibodies used were: Estrogen receptor (ER, clone SP1, 1:50 dilution, Cell Marque, Rocklin, CA, USA), progesterone receptor (PR, clone Y85, 1:40 dilution, Cell Marque, Rocklin, CA, USA), and androgen receptor (AR, clone AR441, 1:100 dilution, Thermo-Scientific, Fremont, CA). Select cases had IHC staining for cytokeratin 5/6 (CK 5/6, clone D5/16B4, Ventana Medical Systems, Tucson, AZ). Staining was performed on the Dako Autostainer platform (Agilent Technologies, Santa Clara, CA), according to the manufacturer's instructions, with appropriate controls.

ER, PR and AR staining in gynecomastoid change was scored by a breast pathologist (JMJ) and reported via the Allred scoring system, adding intensity (negative, 0; weak, 1; intermediate, 2; strong, 3) and proportion scores (none positive, 0; ≤1%, 1; 1-10%, 2, 11-33%, 3; 34-66%, 4; 67-100%, 5) to generate a sum score (with scores of 0-2 interpreted as negative and 3-8 as positive. Background uninvolved (non-gynecomastoid) glands served as internal controls.

Statistical Analysis

Descriptive statistics were presented, which included continuous data (mean and range) and categorical data (frequency and percentage). A simple logistic regression model was used to associate clinical, gross, and histopathologic findings to gynecomastoid change. A multivariate logistic regression model was generated for the outcome of gynecomastoid change using variables for age, BMI, smoking status, number of TDLUs, mean gross fibrous density, total specimen weight, and the use and duration of androgen therapy. Two-way interactions for TDLUs and mean gross fibrous density, mean gross fibrous

density and androgen use, and mean gross fibrous density and BMI were included. A stepwise variable selection procedure was used to select important variables to be included in final logistic regression model (a significance level of 0.35 was used to allow a variable into the model, and a significance level of 0.20 was used for a variable to stay in the model). The final model included BMI and TDLU (0-3). A $p \leq 0.05$ was considered to be statistically significant. All analyses were conducted using SAS (version 9.4, SAS Institute, Cary, NC).

**Results**

Patients

A total of 68 cases (67 patients with simple mastectomy and free nipple grafting, 1 with re-excision) of FTM with breast tissue resection were identified. The mean age at the time of surgery was 31.5 years (range 19-57). Most patients (60/67, 89.6%) had undergone androgen therapy prior to surgery. Two patients had undergone pregnancy and childbirth prior to FTM transition. Family history was available for 66 (98.5%) patients, and was significant for breast cancer in a single relative in 13 (19.7%) patients and ovarian cancer in a single relative in 1 (1.5%) patient. Breast imaging prior to surgery was infrequent (8/67; 11.9%) (Table 1) and benign for all patients; for 6 (75%) the indication was for routine screening and for 1 (12.5%) there was a palpable lesion for which biopsy resulted in the diagnosis of fibroadenoma (1; 12.5% unknown).

Gross Findings

Specimen weight was recorded in the majority of cases with a mean total weight of 1100.2 grams. Mean gross fibrous density was 26.3%. A median of 6 (range 2-20) tissue pieces were submitted in a median of 2 (range 2-16) cassettes per case. Gross lesions were infrequently identified (13/68; 19.1%) (Table 1).

Histologic Findings

TDLUs were absent in 11.8% (8/68), rare in 27.9% (19/68) and frequent in 60.3% (41/68) of cases. Diagnostic findings were present in 75% (51/68) of cases. Fibrocystic changes (27/68; 39.7%) were most frequent (Table 1, Figure 1). Univariate analysis demonstrated fibrocystic changes to be significantly associated with the presence of frequent TDLUs (p=0.0055).

Gynecomatoid change was present in 22 (32.4%) patients, with all cases having features characteristic of those seen in the fibrotic stage of gynecomastia of the male breast, including atrophic duct epithelium and periductal hyalinization and fibrosis (Figures 1-2). Univariate analysis showed gynecomastoid change to be significantly associated with younger age (p=0.0402), lower BMI (p=0.0169), increased gross fibrous density (p=0.0087), increased total specimen weight (p=0.0376), and absent or rare TDLUs

(p=0.0003). Multivariate analysis showed gynecomastoid change to be significantly associated with absent or rare TDLUs (p=0.0016) and lower BMI (p=0.0087).

No specific histologic feature was significantly associated with gross findings or sampling greater numbers of tissue pieces or cassettes.

Immunohistochemistry

IHC performed on 22 cases of gynecomastoid change showed a moderate proportion of strong intensity glandular staining with ER, PR and AR. Specifically, for ER, median Allred score was 6 with range of 5-7, for PR median Allred score was 6, with range of 4-7, and for AR, median Allred score was 6 with range of 4-7. The mean AR:ER Allred score ratio was 0.9 (range 0.7-1.0) (Figure 2, A-D). CK 5/6 IHC performed on 8 blocks with gynecomastoid change showed positive staining in the outer myoepithelial and inner ductal epithelial layers, with no staining in a discontinuous intermediate epithelial layer (Figure 2, E-F).

**Discussion**

Here we present a comprehensive immunomorphologic study of FTM breast resection specimens and identify features unique to these uncommon specimens. These specimens provide insight into androgen-stimulated breast tissue in a unique patient population.

Benign breast disease, particularly fibrocystic change, is a common finding identified in up to 58.5% of asymptomatic women.[16, 17] In this study we identified fibrocystic change in 39.7% of FTM specimens, similar to that noted by Kuroda et al[18] (60/186; 32.3%). In post-menopausal women receiving estrogens for ≥8 years, the prevalence of fibrocystic change is increased 1.7 fold, supporting a role for increased estrogenic states contributing to the development of fibrocystic change.[19] As increased BMI is associated with an increased estrogenic state, and TDLU development is partially driven by the influence of estrogen, the association of fibrocystic change in FTM patients with increased BMI and increased TDLUs is anticipated.[16, 20-22]

Gynecomastia-like hyperplasia has been described as a proliferative lesion of the female breast with histologic features typical of gynecomastia of the male breast.[23, 24] However, unlike fibrocystic disease, the frequent finding of gynecomastoid change in 32.4% of FTM patients is unusual considering its otherwise rare existence in female patients, with previously reported incidences of 0.15% and 0.56%.[24, 25] In our study, all cases with gynecomastoid change had findings identical to that seen in the fibrotic stage of male gynecomastia. Previous studies of FTM breast tissue resection primarily note fibrocystic changes as well as fibrosis and involutionary changes or lobular atrophy.[15, 18, 26-27] Fibrotic stage

gynecomastoid change seen in our study may be associated with and/or represent an end-stage histologic finding as part of the spectrum of fibrosis and atrophy described previously.

The majority of FTM patients, including all 22 with gynecomastoid change, had undergone some duration of androgen therapy. We did not find a statistically-significant correlation between gynecomastoid change and androgen therapy use or duration. However, we found gynecomastoid change to be significantly associated with lower BMI, which is likely explained by increased exogenous androgen and reduced endogenous estrogen as cross-sex hormone therapy is known to increase total body weight and lean body mass in FTM patients.[28] In this study it was difficult to assess overall cumulative dose of exogenous androgens as some patients had received these therapies elsewhere, had intermittent use due to lack of insurance coverage, and had variable documentation of dosing in available clinical notes. This is a noted limitation of this study as degree of androgen exposure is likely a key factor, in addition to BMI, resulting in gynecomastoid change in FTM breast tissue.

In light of the increased prevalence of gynecomastoid change in FTM patients, we sought to compare the IHC profile to that of male gynecomastia. Previous reports show gynecomastic breast tissue in male patients to express receptors for estradiol, progesterone and androgens[29-32] and to have a characteristic 3-layered ductal epithelium with an outer myoepithelial and two inner epithelial layers.[33] Benign luminal cells of the breast have been shown to have scattered, strong positivity for AR in a pattern similar to ER, with the majority of those cells demonstrating dual staining with ER and AR.[34] In our study, gynecomastoid change showed consistent positivity for ER and AR in a moderate proportion of cells with strong intensity of staining, consistent with that reported previously. Additionally, we noted the previously-reported 3-layered staining pattern via CK 5/6 IHC in select cases with gynecomastoid change. Overall, the IHC patterns seen in gynecomastoid change in FTM patients parallel those reported in male gynecomastic tissue.

Our findings support the continued gross and microscopic evaluation of these unique FTM breast resection specimens, particularly in light of the presence of atypia in one case (1.5%). This is similar to the study by Kuroda et al[18] who noted atypia in 3 (1.6%) and in situ carcinoma in one (0.5%) of 186 Japanese FTM patients undergoing resection of breast tissue. Similarly, resection of clinically benign reduction mammoplasty specimens identifies atypia or carcinoma in 0.16 to 2.1%.[35, 36] Ambaye et. al (2009) prospectively evaluated the submission of additional cassettes of suspicious or fibrous tissue from reduction mammoplasty specimens and found improved detection of atypia and carcinoma in patients over age 40.[37] Although the number of cassettes and number of tissue pieces in our study were

not associated with a particular histologic finding, we recommend targeted sampling in multiple areas of gross fibrous density, as would be done in other benign breast specimens.

As noted above, the main limitation of this study is a lack of data on cumulative androgen exposure. Additionally, larger future studies would be helpful as these surgeries become more frequently performed. Specifically, more data is needed to determine "best practices" for gross sampling of these specimens as well as to determine features that may aid in identifying patients at risk for atypical or malignant pathology.

In summary, we identified unique histologic findings associated with FTM breast resection specimens. Specifically, the relative frequent finding of gynecomastoid change appears to be related to therapeutic alteration of the ratio of (exogenous) androgen and (endogenous) estrogen in many FTM patients. Our findings support the continued gross and histologic evaluation of these uncommon specimens.

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Katherine M. Gast and William M. Kuzon, Jr. collected cases for study and edited the manuscript. Ellen G. East and Julie M. Jorns designed the research study, performed the research and wrote the manuscript. Emily Roberts and Lili Zhao analyzed the data and contributed to writing and editing of the manuscript.

Table 1. Clinicopathologic features of female-to-male transgender-affirming patients who underwent resection of breast tissue. (n=68 unless otherwise stated)

| **Clinical characteristics** | **Value** |
|---|---|
| Age (years), mean (range) | 31.5 (19-57) |
| BMI, mean (range), n=66 | 31.7 (19.2-59.0) |

| | |
|---|---|
| Positive smoking status, n (%), n=66 | 5 (7.6) |
| Androgen therapy, n (%), n=67 | 60 (89.6) |
| Duration (years), mean (range) | 1.89 (0.2-10.0) |
| Prior pregnancy resulting in live birth, n (%), n=67 | 2 (3.0) |
| Prior breast imaging preformed, n (%), n=67 | 8 (11.9) |
| Family history of breast or ovarian cancer, n (%), n=66 | 14 (21.2) |
| Non-first degree relative[1] | 13 (19.7) |
| First degree relative[2] | 1 (1.5) |
| | |
| **Gross characteristics** | **Value** |
| Total weight (g), mean (range) n=61 | 1100.2 (46.5-2890.0) |
| Fibrous density, mean (range), n=53 | 26.3 (3-77.5) |
| Cassettes submitted, median (range) | 2 (2-16) |
| Total pieces submitted, median (range), n=67 | 6 (2-20) |
| Number of TDLUs, n (%) | |
| Absent (0) | 8 (11.8) |
| Rare (1-3) | 19 (27.9) |
| Frequent (>3) | 41 (60.3) |
| Gross lesion identified, any type, n (%) | 13 (19.1) |
| Cysts | 8 (11.8) |
| Nodularity | 3 (4.4) |
| Discoloration | 2 (2.9) |
| | |
| **Histologic characteristics** | **N (%)** |
| Diagnostic finding, any type | 51 (75.0%) |
| Fibrocystic changes | 27 (39.7%) |
| Simple cysts | 22 (32.4%) |
| Apocrine metaplasia | 16 (23.5%) |
| Adenosis | 5 (7.4%) |
| Usual ductal hyperplasia | 3 (4.4%) |
| Gynecomastoid change, fibrotic stage | 22 (32.4%) |
| Fibroadenomatoid change | 11 (16.2%) |

| | |
|---|---|
| Duct ectasia | 12 (17.6%) |
| Lactational changes | 2 (2.9%) |
| Intraductal papilloma | 1 (1.5%) |
| Flat epithelial atypia | 1 (1.5%) |

BMI, body mass index; TDLUs, terminal duct lobular units

[1]Breast cancer (n=12), ovarian cancer (n=1)

[2]Breast cancer in mother (post-menopausal)

Table 2. Features associated with gynecomastoid change.

| **Clinicopathologic Feature** | | **Odds Ratio (95% CI)** | **p value** |
|---|---|---|---|
| Univariate | BMI | 0.901 (0.828, 0.981) | 0.0169 |
| | Age | 0.931 (0.869, 0.997) | 0.0402 |
| | Gross fibrous density | 1.044 (1.011, 1.078) | 0.0087 |
| | Total specimen weight | 0.999 (0.998, 1.000) | 0.0376 |
| | Absent-rare TDLUs | 8.484 (2.667, 26.990) | 0.0003 |
| Multivariate, n=48 | BMI | 0.826 (0.717, 0.953) | 0.0087 |
| | Absent-rare TDLUs | 21.347 (3.187, 142.981) | 0.0016 |

BMI, body mass index; TDLUs, terminal duct lobular units

**Figure legends**:

**Figure 1.** Histologic findings in female-to-male breast resection specimens. Flat epithelial atypia, 20X (A), gynecomastoid change, 10X (B), fibroadenomatoid change, 10X (C), apocrine metaplasia, 10X (D), simple cysts, 10X (E), and duct ectasia, 10X (F).

**Figure 2.** Gynecomastoid change, 20X (A), with ER, 20X (B) (proportion 3, intensity 3) , PR, 20X (C) (proportion 2, intensity 3), and AR, 20X (D) (proportion 3, intensity 3) immunohistochemical staining. Gynecomastoid change, 20X (E), with cytokeratin 5/6 immunohistochemistry highlighting the outer myoepithelial and inner ductal epithelial layers, with no staining in the intermediate epithelial layer, 20X (F).

**References:**

1. American Psychiatric Association., American Psychiatric Association. DSM-5 Task Force. *Diagnostic and statistical manual of mental disorders : Dsm-5*. 5th ed. Arlington, VA: American Psychiatric Association, 2013;xliv, 947 p.

2. Dhejne C, Oberg K, Arver S, Landen M. An analysis of all applications for sex reassignment surgery in sweden, 1960-2010: Prevalence, incidence, and regrets. *Arch Sex Behav* 2014;**43**;1535-1545.

3. Gomez-Gil E, Trilla A, Salamero M, Godas T, Valdes M. Sociodemographic, clinical, and psychiatric characteristics of transsexuals from spain. *Arch Sex Behav* 2009;**38**;378-392.

4. Hoenig J, Kenna JC. The prevalence of transsexualism in england and wales. *Br J Psychiatry* 1974;**124**;181-190.

5. Landen M, Walinder J, Lundstrom B. Prevalence, incidence and sex ratio of transsexualism. *Acta Psychiatr Scand* 1996;**93**;221-223.

6. Olsson SE, Moller AR. On the incidence and sex ratio of transsexualism in sweden, 1972-2002. *Arch Sex Behav* 2003;**32**;381-386.

7. Ross MW, Walinder J, Lundstrom B, Thuwe I. Cross-cultural approaches to transsexualism. A comparison between sweden and australia. *Acta Psychiatr Scand* 1981;**63**;75-82.

8. Sorensen T, Hertoft P. Male and female transsexualism: The danish experience with 37 patients. *Arch Sex Behav* 1982;**11**;133-155.

9. Walinder J. Incidence and sex ratio of transsexualism in sweden. *Br J Psychiatry* 1971;**119**;195-196.

10. Weitze C, Osburg S. Transsexualism in germany: Empirical data on epidemiology and application of the german transsexuals' act during its first ten years. *Arch Sex Behav* 1996;**25**;409-425.

11. Flores AR, Herman JL, Gates GJ, Brown TNT. How many adults identify as transgender in the united states? The Williams Institue https://williamsinstitute.law.ucla.edu/wp-content/uploads/How-Many-Adults-Identify-as-Transgender-in-the-United-States.pdf., 2016.

12. Herman JL, Flores AR, Brown TNT, Wilson BDM, Conron KJ. Age of individuals who identify as transgender in the united states. The Williams Institute https://williamsinstitute.law.ucla.edu/wp-content/uploads/TransAgeReport.pdf., 2017.

13. Monstrey S, Hoebeke P, Dhont M *et al.* Surgical therapy in transsexual patients: A multi-disciplinary approach. *Acta Chir Belg* 2001;**101**;200-209.

14. World professional association for transgender health. Standards of care for the health of transsexual, transgender, and gender nonconforming people. Version 7. Http://www.Wpath.Org/site_page.Cfm?Pk_association_webpage_menu=1351&pk_association_webpage=3926., 2012.

15. Grynberg M, Fanchin R, Dubost G *et al.* Histology of genital tract and breast tissue after long-term testosterone administration in a female-to-male transsexual population. *Reprod Biomed Online* 2010;**20**;553-558.

16. Goehring C, Morabia A. Epidemiology of benign breast disease, with special attention to histologic types. *Epidemiol Rev* 1997;**19**;310-327.

17. Davis HH, Simons M, Davis JB. Cystic disease of the breast: Relationship to carcinoma. *Cancer* 1964;**17**;957-978.

18. Kuroda H, Ohnisi K, Sakamoto G, Itoyama S. Clinicopathological study of breast tissue in female-to-male transsexuals. *Surg Today* 2008;**38**:1067-1071.

19. Rohan TE, Negassa A, Chlebowski RT *et al.* Estrogen plus progestin and risk of benign proliferative breast disease. *Cancer Epidemiol Biomarkers Prev* 2008;**17**;2337-2343.

20. McDivitt RW, Stevens JA, Lee NC, Wingo PA, Rubin GL, Gersell D. Histologic types of benign breast disease and the risk for breast cancer. The cancer and steroid hormone study group. *Cancer* 1992;**69**;1408-1414.

21. London SJ, Connolly JL, Schnitt SJ, Colditz GA. A prospective study of benign breast disease and the risk of breast cancer. *JAMA* 1992;**267**;941-944.

22. Santen RJ. Benign breast disease in women. In De Groot LJ, Chrousos G, Dungan K *et al.* eds. *Endotext*. South Dartmouth (MA), 2000.

23. Rosen PP. *Rosen's breast pathology*. Philadelphia, PA: Lippincott Williams & Wilkins, 2008.

24. Umlas J. Gynecomastia-like lesions in the female breast. *Arch Pathol Lab Med* 2000;**124**;844-847.

25. Kang Y, Wile M, Schinella R. Gynecomastia-like changes of the female breast. *Arch Pathol Lab Med* 2001;**125**;506-509.

26. Burgess HE, Shousha S. An immunohistochemical study of the long-term effects of androgen administration on female-to-male transsexual breast: A comparison with normal female breast and male breast showing gynaecomastia. *J Pathol* 1992;**170**:37-43.

27. Slagter MH, Gooren LJG, Scorilas A, Petraki CD, Diamandis EP. Effects of long-term androgen administration on breast tissue of female-to-male transsexuals. 2006;**54**:905-910.

28. Klaver M, Dekker MJ, de Mutsert R, Twisk JW, den Heijer M. Cross-sex hormone therapy in transgender persons affects total body weight, body fat and lean body mass: A meta-analysis. *Andrologia* 2016.

29. Grilli S, De Giovanni C, Galli MC *et al.* The simultaneous occurrence of cytoplasmic receptors for various steroid hormones in male breast carcinoma and gynaecomastia. *J Steroid Biochem* 1980;**13**;813-820.

30. Pacheco MM, Oshima CF, Lopes MP, Widman A, Franco EL, Brentani MM. Steroid hormone receptors in male breast diseases. *Anticancer Res* 1986;**6**;1013-1017.

31. Rosen PP, Menendez-Botet CJ, Nisselbaum JS, Schwartz MK, Urban JA. Estrogen receptor protein in lesions of the male breast: A preliminary report. *Cancer* 1976;**37**;1866-1868.

32. Kraus TS, Cohen C, Siddiqui MT. Prostate-specific antigen and hormone receptor expression in male and female breast carcinoma. *Diagn Pathol* 2010;**5**;63.

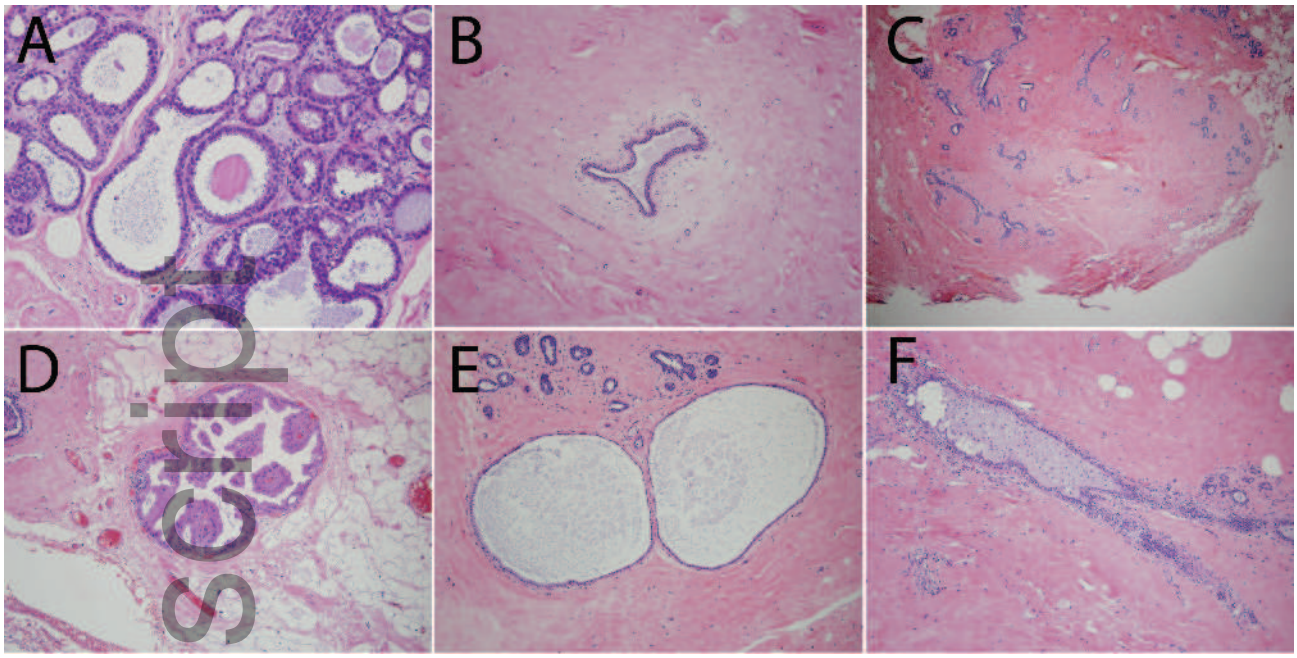
33. Kornegoor R, Vershuur-Maes AHJ, Buerger H, Van Diest PJ. The 3-layered ductal epithelium in Gynecomastia. *Am J Surg Pathol.* 2012;**36**:762-768.

34. Wang X, Yarid N, McMahon L, Yang Q, Hicks DG. Expression of androgen receptor and its association with estrogen receptor and androgen receptor downstream proteins in normal/benign breast luminal epithelium. *Appl Immunohistochem Mol Morphol* 2014;**22**;498-504.

35. Ishag MT, Bashinsky DY, Beliaeva IV, Niemann TH, Marsh WL, Jr. Pathologic findings in reduction mammaplasty specimens. *Am J Clin Pathol* 2003;**120**;377-380.

36. Jansen DA, Murphy M, Kind GM, Sands K. Breast cancer in reduction mammoplasty: Case reports and a survey of plastic surgeons. *Plast Reconstr Surg* 1998;**101**;361-364.

37. Ambaye AB, MacLennan SE, Goodwin AJ, Suppan T, Naud S, Weaver DL. Carcinoma and atypical hyperplasia in reduction mammaplasty: Increased sampling leads to increased detection. A prospective study. *Plast Reconstr Surg* 2009;**124**;1386-1392.

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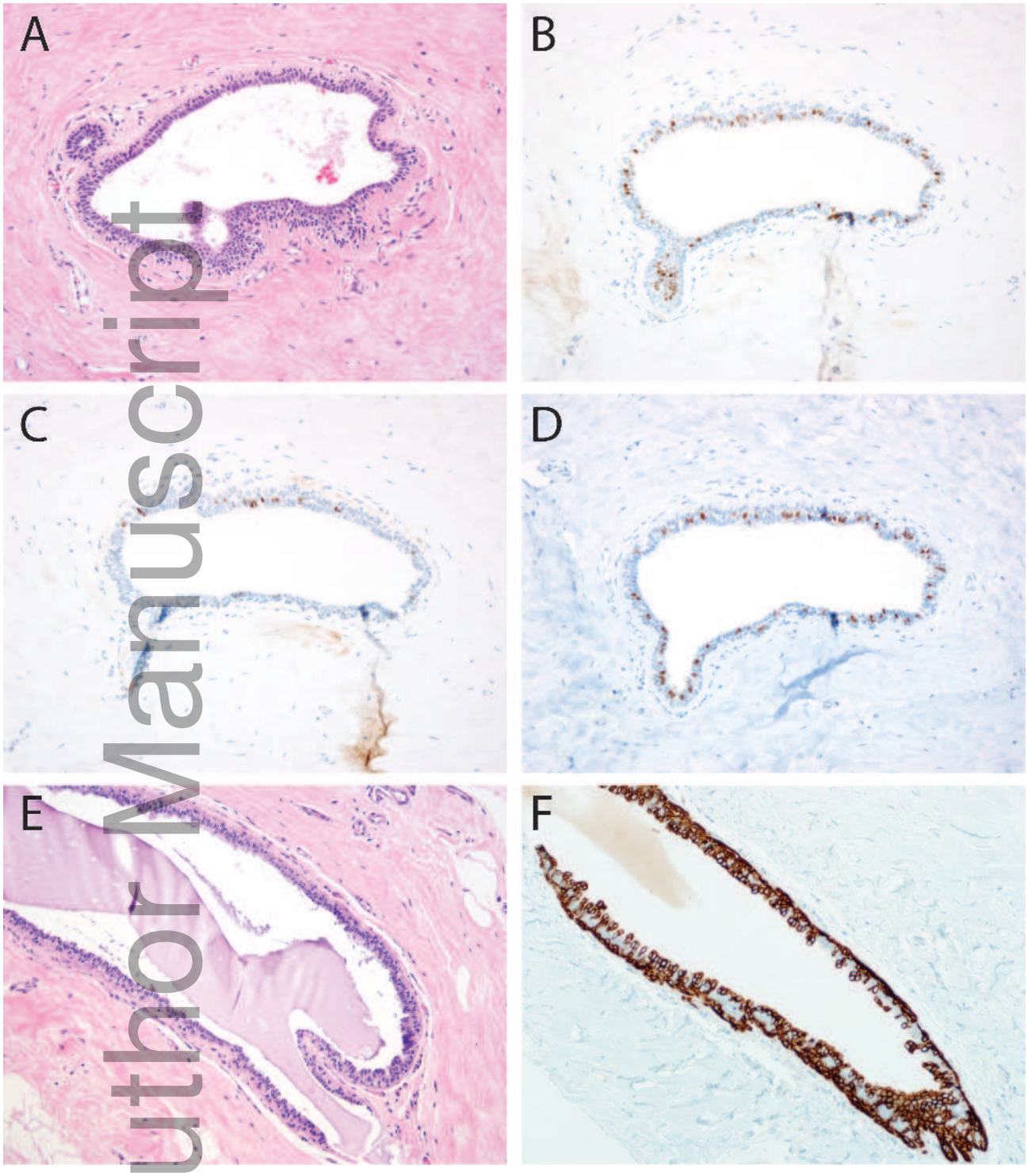




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