

Testis Morphologic Assessment in Patients undergoing Sex Reassignment Surgery with Gender Dysphoria: Case Series and Literature Review

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Abstract

Purpose: To study the morphologic changes to testicular architecture in response to estrogen therapy in gender dysphoric patients undergoing sexual reassignment surgery.

Materials and methods: A retrospective morphologic review of testicular architecture was performed on ten cases of male-to-female sex reassignment surgery testis from the University of Illinois Hospital and Health Sciences system. Cases were from adult males undergoing sexual reassignment surgery at the University of Illinois Hospital and Health Sciences System between 2016 and 2017. Architectural changes were measured including Leydig cell changes, basement membrane fibrosis, spermatogonia maturation, and interstitium changes.

Results: Various stages of maturation and regression were seen despite all patients being on estrogen therapy for at least one year prior to undergoing surgery.

Conclusion: There are a range of estrogen therapy-related maturation and regression effects on testicular architecture in this growing patient population. It is important for the clinician and pathologist to know these effects as benign changes related to treatment.

Keywords: Gender dysphoria; Surgery; Maturation; Estrogen therapy, Testis

Introduction

Gender dysphoria or gender identity disorder (GID) is defined as the distress a person experiences as a result of the sex and gender they were assigned at birth. In these cases, the assigned sex and gender do not match the person's gender identity, and the person is socially identified as transgender. The DSM-V indicates that the prevalence of gender dysphoria is 0.005%-0.014% for adults born as males, and it is 0.002%-0.003% for adults born as females [1].

The American Psychiatric Association permits a diagnosis of gender dysphoria if the criteria in the DSM-V are met. The criteria apply to adolescents and adults that have at least two of the following over the course of six months.

A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics

A strong desire to be rid of one's primary and/or secondary sex characteristics

A strong desire for the primary and/or secondary sex characteristics of the other gender

A strong desire to be of the other gender

A strong desire to be treated as the other gender

A strong conviction that one has the typical feelings and reactions of the other gender [2].

There is evidence suggesting that twins who identify with a gender different from the one they were assigned at birth may do so not just due to psychological or behavioral causes, but also biological ones related to their genetics or exposure to hormones before birth [3].

Treatment for gender dysphoria consists of psychotherapy, pharmacologic therapy and other therapies. Hormonal therapy is given to suppress the endogenous hormones produced and administer exogenous doses of normal hormones of the opposite sex in appropriate dosages [4]. Sexual reassignment surgery (SRS), also referred to as gender confirmation surgery, is the final step toward physical adaptation. There are strict requirements that must be met prior to undergoing SRS. The patient must have been consistently compliant with hormone therapy for at least a year and have been actively undergoing psychotherapy during this period. During this time, the patient must have a social role change, be satisfied with hormonal effects and desire definitive surgical changes [4]. When changing anatomical sexual characteristics from male to female, the testes are removed, and the most common technique used is inverting the foreskin and skin from the penis as a flap preserving blood and nerve supplies to form a fully sensitive vagina (vaginoplasty) [5].

Although the number of transgender surgeries has been dramatically increased in the last few years, there have been few reported studies determining the mechanism behind differing testicular histology or reported morphologic differences in patients that undergoing hormonal treatment for gender dysphoria. Estrogen effects of testicular histology have been well described; these findings alone cannot explain the differing histologic features in these SRS patients as seen in one study performed recently [6]. Here we present a

histologic review of 10 patients who underwent male-to-female sex reassignment surgery at the University of Illinois Hospital and Health Sciences system in 2016 and 2017.

Materials and Methods

Retrospective analysis of ten cases of adult male-to-female sex reassignment surgery performed at the University of Illinois Hospital and Health Sciences System were chosen starting from February 2016 to June 2017. Institutional review board (IRB) approval was not performed in this case as this study met the exemption requirements of our institution. The patients chosen had no prior history of testicular disease. Two 5 micron thick Hematoxylin and Eosin stained sections were reviewed per case, one representative section from each testis. Two pathology residents, one junior faculty member, and one senior faculty member reviewed the slides to assess morphologic estrogen effect on spermatocytic development, leydig cells, and fibrosis of the basement membrane. All four reviewers were blinded to the clinical diagnosis for each case when reviewing the slides. The two residents reviewed the slides independently and the two faculty members reviewed the slides together and came to a consensus diagnosis. Histology for Pathologists, second edition was used as a reference for normal testicular morphology.

Results

Estrogen therapy is known to affect testicular architecture in three ways: the maturation of the spermatogonia into spermatids, the number of Leydig cells present in the interstitium and the amount of stromal and basement membrane fibrosis surrounding the tubules. These parts of the testicular architecture were assessed by all pathologists and recorded in a table shared among the pathologists. After review, the investigators discussed any discrepancies and formed a consensus opinion for each specimen which is recorded as the summary of the histologic and morphologic characteristics of the ten cases seen in Table 1. Three cases showed normal spermatocytic maturation, one case showed decreased maturation, three cases

showed maturation arrest with primary spermatocytes present, and three cases showed Sertoli only cell morphology. Only those cases with absent spermatogenesis had basal lamina fibrosis, fibrotic/sclerotic interstitium and absent Leydig cells on Hemotoxylin and Eosin stained sections. Sertoli cells were identified in all cases and appeared to be of normal morphology. Representative images of the various degrees of changes to architecture and morphology are shown in Figure 1.

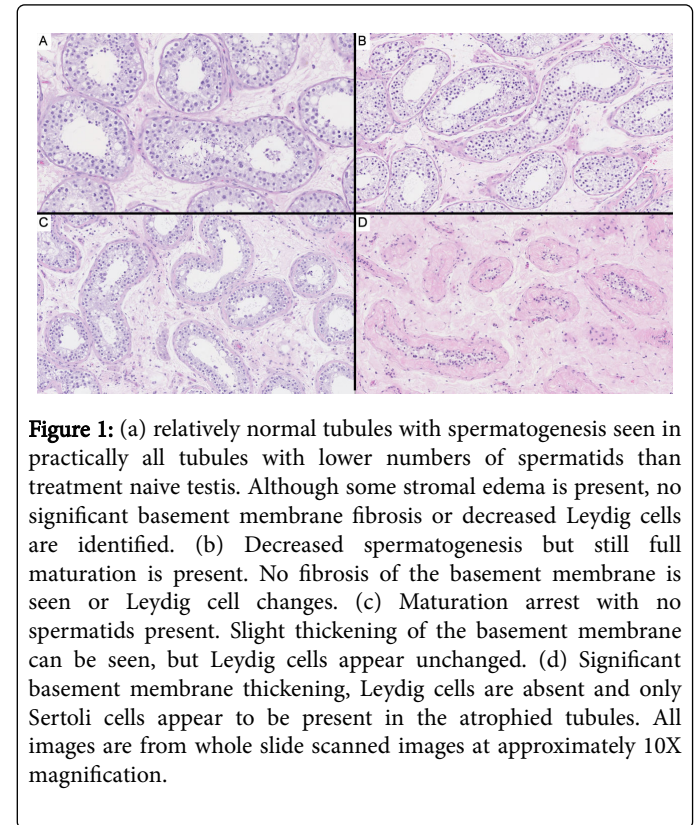


Figure 1: (a) relatively normal tubules with spermatogenesis seen in practically all tubules with lower numbers of spermatids than treatment naive testis. Although some stromal edema is present, no significant basement membrane fibrosis or decreased Leydig cells are identified. (b) Decreased spermatogenesis but still full maturation is present. No fibrosis of the basement membrane is seen or Leydig cell changes. (c) Maturation arrest with no spermatids present. Slight thickening of the basement membrane can be seen, but Leydig cells appear unchanged. (d) Significant basement membrane thickening, Leydig cells are absent and only Sertoli cells appear to be present in the atrophied tubules. All images are from whole slide scanned images at approximately 10X magnification.

Case	Spermatogenesis	Basal lamina fibrosis	Interstitialium	Leydig cells	Sertoli cells
1	Complete spermatogenesis with decreased number of spermatids	Absent	Mild fibrotic changes	Present	Present
2	Absent-tubules with Sertoli cells only	Present	Fibrotic/sclerotic	Absent based on H&E light microscopy	Present
3	Absent-tubules with Sertoli cells only	Present	Fibrotic/sclerotic	Absent based on H&E light microscopy	Present
4	Spermatogonia and primary spermatocytes present without significant numbers of spermatids consistent with maturation arrest	Absent	Mild fibrotic changes	Present	Present
5	Spermatogonia and primary spermatocytes present without significant numbers of spermatids consistent with maturation arrest	Absent	Mild fibrotic changes	Present	Present
6	Absent-tubules with Sertoli cells only	Present	Fibrotic/sclerotic	Absent based on H&E light microscopy	Present
7	Normal spermatogenesis	Absent	No fibrotic changes	Present	Present

8	Spermatogonia and primary spermatocytes present without significant numbers of spermatids consistent with maturation arrest	Absent	Mild fibrosis	Present	Present
9	Normal spermatogenesis with epididymal cribriform hyperplasia	Absent	No fibrotic changes	Present	Present
10	Normal spermatogenesis with epididymal cribriform hyperplasia	Absent	Mild Fibrosis	Present	Present

Table 1: Consensus results of morphologic review of ten cases of bilateral testis from patients with gender reassignment surgery showing various stages of histologic dedifferentiation.

Discussion

Estrogen effects on testicular structure and function have long been known to occur from estrogen treatment of prostatic adenocarcinoma [7]. More recently, transgender patients have begun long-term estrogen therapy as part of the feminization process. Some of these patients ultimately undergo sexual reassignment surgery. In addition to the effects on testicular size and architecture, these patients also show fat redistribution, breast enlargement, and changes in hair distribution from estrogen therapies.

Changes observed in testicular architecture during estrogen therapy include reduced spermatogenesis, seminiferous tubules consisting of Sertoli cells and spermatogonia only (diagnostically maturation arrest) or Sertoli only tubules, reduced Leydig cell numbers and tubular sclerosis; all of which were assessed in this morphologic study. The dosage of estrogen therapy and length of therapy determines the degree of changes identified, based on previous data [8]. In our cohort, estrogen therapy was confirmed in all patients for at least a year, but the dosages and total length of hormonal therapy was not standardized.

The changes seen with estrogen therapy have a similar morphology that reflects reversion of adult testis to infantile testis [8]. During this process of regression, the morphology of these testes passes through the various normal stages of development in reverse. So much so that many times these testes can be classified as testis with complete, but decreased maturation (i.e. normal for age), pubertal-like seminiferous tubules (containing spermatogonia and Sertoli cells only), and infantile testis (Sertoli only or spermatogonia only) [7].

Early ultrastructural studies by light and electron microscopy have been performed on the various elements of the testis in order to better understand the underlying processes of the changes that occur with estrogen therapy. A study by Payer et al. showed the dedifferentiation process of Leydig cells in transgender patients undergoing sexual reassignment surgery [9]. This paper classified the Leydig cells into three groups based on light and electron microscopic structure. The cells appeared to represent different stages of Leydig cell differentiation during embryogenesis. Additional studies have shown that the Leydig cells, Sertoli cells, and spermatogonia undergo a dedifferentiation process that leads to immature testis appearance and the amount of immaturity is related to length of estrogen treatment. Interestingly, this theory of dedifferentiation has been illustrated and supported by immunohistochemical studies showing positivity of Sertoli cells to sialo-glycoprotein M2A (a marker usually lost after 2 years of age) in cases of testes reflecting a pre-pubertal state on light microscopy [10].

In view of the currently increasing number of transgender patients undergoing sexual reassignment surgery, it is important for the surgical pathologist to recognize the varying morphologies that may be seen in these patients. Previous morphologic assessments in these patients have been scarce, and show varying results. In small cohort studies, uniform spermatogonial arrest and varying degrees of spermatogenic impairment have been reported [11]. A larger study by Schnedier et al. showed heterogeneous results in the degree of spermatogenesis [6]. To date, only one recent morphologic study assessing spermatogenesis and premalignant potential has been described [12]. In this study by Kent et al., 135 orchiectomy specimens from gender reassignment surgeries showed various stages of spermatogenesis regression and none of the cases showed premalignant changes. Although many of these studies have clinical data about the dosage and duration of estrogen treatment, our patients do not have their treatment regimens documented in their chart as their psychiatric care is given outside the university setting. Fibrosis and Leydig cell changes have not been assessed in other studies. Additional information on why the heterogeneity of morphology is seen in these patients is necessary to elucidate the details of the underlying functional pathway of estrogen therapy in this patient population.

Conclusion

Differing testicular histomorphology has been previously identified in patients undergoing estrogen therapies for prostatic cancer. Rare reports of similar testicular regression have been seen in gender dysphoric patients undergoing sexual reassignment surgery. Our case series contributes to the literature more data on this topic and suggests further research is needed to understand why there are differences in morphological response to estrogen treatment in this patient population.

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