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Exploring the Incidence of Testicular Neoplasms in the Transgender Population

A Case Series

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• ***Context.***—**The use of hormonal therapy and gender-affirming surgery in the transgender community has been rising during the last several years. Although it is generally safe, hormonal therapy's link to testicular cancer remains uncertain.**

Objective.—**To review the incidence of testicular cancer in specimens from gender-affirming orchiectomies at our institution and evaluate the tumors for histologic and genetic alterations.**

Design.—**Pathology reports for gender-affirming orchiectomies (January 1, 2018, to August 1, 2023) were reviewed for testicular neoplasms, with additional analysis for chromosome 12 abnormalities. Incidence and chromosome variations were compared with those in the general population.**

Results.—**Among 458 cases during 5.5 years, 5 germ cell neoplasms in 4 patients emerged. Our institution's annual incidence rate (159 per 100 000) is 26.5 times higher than the National Cancer Institute's previous report (6.0 per 100 000). Although they were morphologically no different from germ cell neoplasms in the general population, fluorescence in situ hybridization tests showed no i(12p) in 4 of 5 neoplasms (80%) in our cohort.**

Conclusions.—**The cause behind this rise in incidence remains uncertain but may be due to long term pretreatment with hormones or blockers. The lower isochromosome 12p frequency suggests an alternative mechanism driving tumor development, which requires more detailed molecular studies.**

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Testicular cancer is a relatively rare but significant malignancy that represents approximately 1% of all adult neoplasms.[1,2] The incidence rate in the United States approaches 6.0 in 100 000 annually.[2] In young men, testicular cancer is among the most common malignancies, with more than 57% of new cases occurring before age 35.[2] Understanding its incidence, both within the broader population and in certain at-risk groups, is crucial in order to design preventative health care strategies.

Assessing testicular cancer incidence among transgender individuals can be challenging because of limited data and the complex landscape of transgender health care.[1,3,4] Several preliminary studies have suggested that the incidence in transgender populations does not differ significantly from that in cisgender males.[3,5] However, comprehensive, large-scale studies are needed to establish concrete conclusions and explore potential risk factors within this demographic.

With a growing number of adults identifying as transgender, and rates climbing each year, it is more important than ever to delineate the elements that increase cancer risk. Cross-hormonal therapy is generally accepted as safe, yet the risk of development of testicular cancer is not well established.[5–8] Conversely, gender confirmation surgeries have been shown to improve mental health outcomes for transgender individuals, including improved quality of life, body image, and overall self-esteem.[9-11] Many adults undergoing transition choose to pursue orchiectomy, leaving pathology laboratories with the responsibility of handling removed testicular specimens. The subsequent guidelines for both gross and histologic evaluations of these specimens remain uncertain, and there have been several cases of incidental neoplasms found on routine assessment.[3,12–17] Furthermore, from the specimens analyzed so far, it is clear that hormone therapy has unequivocal effects on tissue architecture, as evidenced by microscopic findings showcasing discernible alterations in cellular structures, organization, and overall tissue morphology. Specifically, feminizing hormone therapy has demonstrated histologic changes including cytoplasmic vacuolization, maturation arrest, basement membrane thickening, tubular atrophy, and decreased Leydig cell counts within testicular tissue.[18]

Of note, atypical germ cells, similar to the entity seen in undescended testis, infertility, or sex development disorders, have recently been identified in orchiectomy specimens from transgender patients with prolonged hormonal therapy.[19,20] These cells frequently have large or irregular binucleation with coarse chromatin.[21,22] These features likely represent degenerative changes and are not thought to be a precursor

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lesion for germ cell tumors (GCTs); however, there is some concern for increased malignant transformation, especially because germ cells of similar morphology have already demonstrated such risk.[19,20,23] Because of the significant impact on tissue structure, further studies and careful clinical follow-up are warranted for patients in whom this atypia is identified.

Genetic profiles of invasive testicular GCTs are heterogenous. However, nearly all GCTs in postpubertal individuals have an isochromosome of 12p on chromosomal analysis.[24] However, the influence of hormone therapy on this genetic profile remains a subject of active inquiry. There is speculation regarding whether hormone therapy might influence the genetic landscape of testicular cancer. Research to explore whether hormone-induced shifts could potentially modify the characteristics or expression patterns of testicular cancer subtypes is ongoing. Understanding these potential alterations could provide valuable insights into the interplay between hormone therapy and the genetic makeup of GCTs, contributing to more personalized and effective treatment approaches.

In this report, we review the incidence of testicular cancer in specimens from gender-affirming orchiectomies at our institution and compare it with the at-risk population while also evaluating the tumors for histologic and genetic alterations.

DESIGN

Our data collection was designed to ensure a comprehensive retrieval of retrospective information regarding orchiectomies performed for gender dysphoria at our institution between January 1, 2018 and August 1, 2023. Epic Beaker and PowerPath, our electronic medical record systems during this period, were used to identify cases meeting these criteria for inclusion. The search parameters were created to capture patients who underwent orchiectomies explicitly for gender affirmation purposes, as opposed to concern for malignancy. The specific criteria used included searching keywords for component (testes, testis, orchi*), procedure (orchiectomy, vaginoplasty) or diagnosis (gender dysphoria, gender affirmation). Once identified, the pathology reports and corresponding slides were reviewed to identify and classify cases of testicular neoplasms, ensuring that only relevant cases were included in our analysis.

The incidence rate was then calculated by dividing the number of cases we identified by the total number of specimens examined, expressed in 100 000 patient-years. From this, we were able to determine the standardized incidence ratio (SIR) by comparing the incidence from the study with the expected number of cases in the reference population (which, in this case, was the general US population). Information obtained from previously published data by the National Cancer Institute was used to derive the incidence rates of testicular neoplasms within the reference group. The SIR with a 95% CI was calculated using a midexact *P* test on OpenEpi version 3.01 (www.OpenEpi.com).

The identification of genetic variants in chromosome 12 was conducted via fluorescence in situ hybridization (FISH) and/or chromosomal microarray analysis (CMA). FISH probes are designed to bind to precise target sequences within chromosome 12 or its translocated segments. This specificity enables the accurate localization of the translocation breakpoints.[25] CMA, a powerful technology used in detecting copy number variations and large-scale chromosomal alterations,[25] was performed at Mayo Clinic Laboratory (Rochester, Minnesota). Interpretation of chromosome 12 variations is important to highlight significant differences from normal genome or expression patterns in testicular cancers so far identified. These findings contributed to the understanding of tumorigenesis of testicular neoplasms in the transgender population.

Measures were taken to ensure patient privacy throughout the study. Personal information, including identifying details such as names, addresses, and medical record numbers, was systematically removed or encrypted from the data collection forms used for analysis. Additionally, access to any potentially identifying information was restricted to authorized personnel involved in the study, maintaining strict confidentiality and compliance with privacy regulations to prevent any reidentification of individuals.

RESULTS

The orchiectomy specimens were thoroughly sectioned at 3-mm intervals to identify gross abnormalities. Two representative sections were submitted for routine hematoxylin-eosin microscopic examination in cases with no gross abnormality. More than 98.5% (452 of 458) of specimens reviewed in this study displayed changes consistent with feminizing hormone therapy, including hypospermatogenesis, atrophy, degenerative changes (including nuclear atypia), and maturation arrest (Figure 1, A through D). Five testicular tumors in 4 patients, 1 of whom had bilateral disease, were identified from a total of 458 specimens (458 patients, 916 testicles) obtained from gender-affirming orchiectomies in a 5.5-year span. The neoplasms consisted of embryonal carcinoma with minor yolk sac component (case 1; Figure 2, A and B), bilateral seminoma (case 2; Figure 2, C and D), extensive germ cell in situ (case 3; Figure 3, A through C), and finally teratoma with minor seminoma (case 4; Figure 3, D through F).

Table 1 summarizes each of these neoplasms. Of the cases identified, only case 2 had a questionable history of neoplasia—presenting previously with a pituitary mass, currently under surveillance. None of the other cases had pertinent medical history. Interestingly, all 4 trans women had been on a hormonal therapy regimen for at least 2 years. Each patient had been undergoing gender-affirming hormonal therapy (GAHT) for 2, 4, 2.5, and 2 years, respectively, with exogenous estrogen in the form of patches or oral medication. GAHT also included antiandrogenic treatment (ie, spironolactone) in case 1 and progesterone in cases 3 and 4. The highest tumor stage of the cases identified was T2 (case 1), with 2 others in stage T1 (cases 2 and 4) and 1 case of in situ disease (case 3). All remained clinically stable after the time of diagnosis/treatment. Table 2 summarizes the gross, microscopic, and molecular characteristics of each tumor. The cases present a range of characteristics. Case 1 involved a tumor measuring 1.3 × 1.0 × 0.8 cm that was submitted in 24 blocks. The tumor was confined to the testis, and was associated with background germ cell neoplasia in situ (GCNIS) and a hormone treatment effect. It was predominantly composed of embryonal (95%) and yolk sac (5%) components and had no isochromosome 12p detected on FISH. In case 2, no discrete nodule was identified. The specimen was submitted in 10 blocks. Microscopic analysis featured seminoma only with tumor invasion into the rete testis (testis A) and without rete testis invasion (testis B) along with GCNIS and hormone treatment effect. Once again, there was no isochromosome 12p detected on FISH. Case 3 presented as a tumor, 0.5 × 0.5 ×

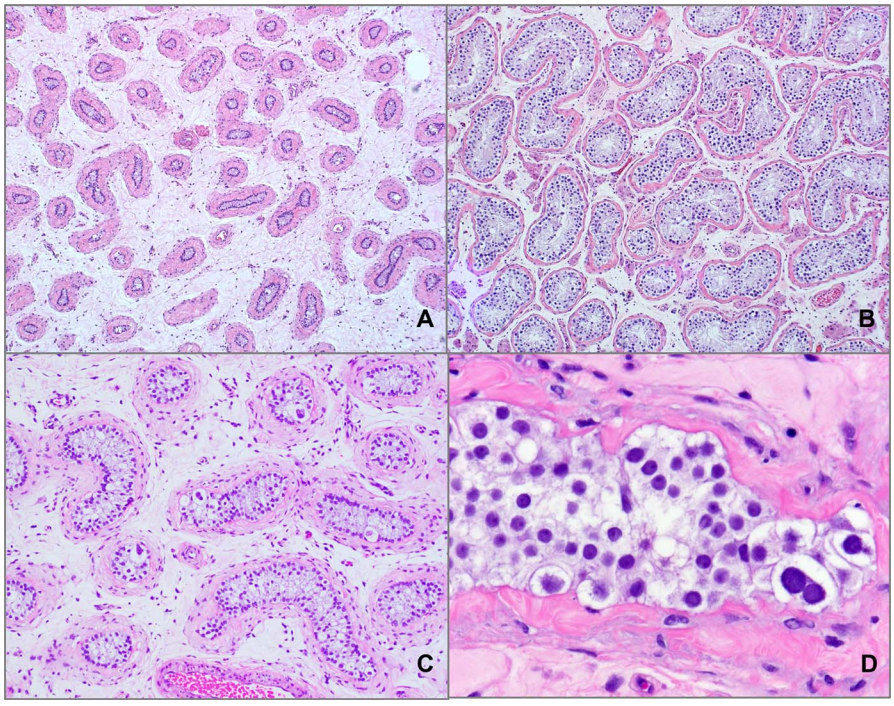

Figure 1. *General changes common in hormone-treated specimens. Hematoxylin-eosin stain of testis with atrophy (A). Hematoxylin-eosin stain of testis with mild atrophy and maturation arrest (B). Hematoxylin-eosin stain of atypical germ cells with binucleation at low power (C) and high power (D) (original magnifications ×4 [A and B], ×10 [C], and ×20 [D]).*

0.4 cm, submitted in 8 blocks. There was extensive GCNIS that was confined to the testis alongside hormone treatment effect. Lastly, case 4 exhibited a tumor measuring 1.3 × 0.9 × 0.7 cm. Seven blocks were submitted for this specimen. It was primarily composed of a teratoma component (90%) and seminoma (10%), accompanied by GCNIS and a hormone treatment effect. Isochromosome 12p was detected only in this neoplasm.

The immunohistochemistry findings across the cases reveal diverse staining profiles. In case 1, the embryonal component shows positivity for OCT-4, CD30, and CAM5.2, while testing negative for glypican 3, GATA3, and CD117. Conversely, the yolk sac component exhibits positivity for glypican 3 and AFP but is negative for OCT-4. Additionally, OCT-4 and CD117 highlight GCNIS. In case 2, CD117, Oct-4, and SALL4 are positive, with glypican 3 testing negative. Case 3 displays positivity for OCT3/4. Case 4 reveals diffuse positivity for CD117, Oct-4, and SALL4 in the seminoma component, whereas the teratoma component tests negative for these markers.

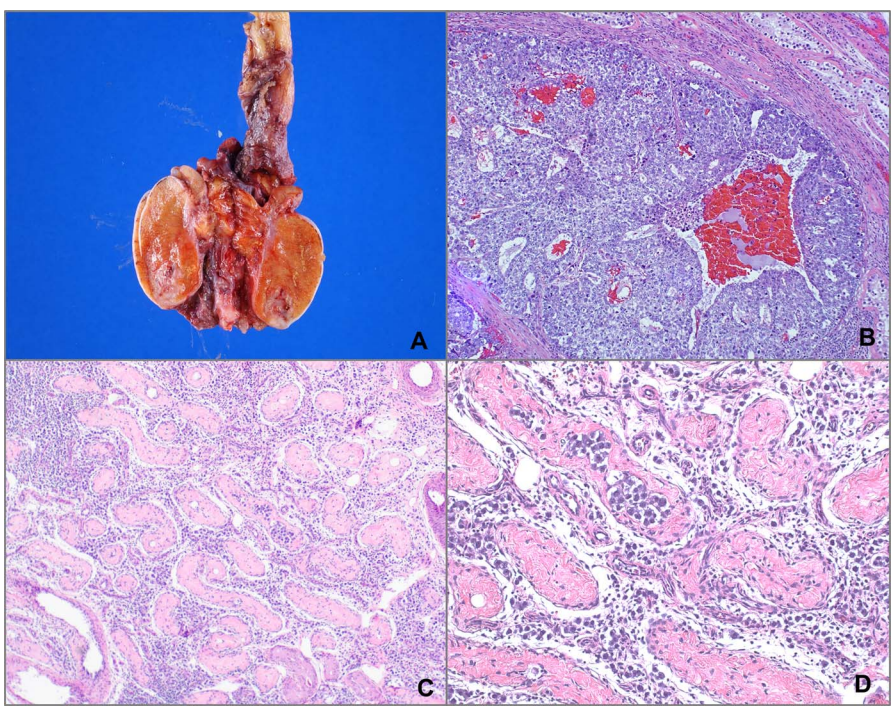

Figure 2. *Case 1. Gross image of testes from gender-affirming orchiectomy with incidental mixed germ cell tumor (A). Hematoxylin-eosin stain of mixed germ cell tumor with primarily embryonal carcinoma with minor yolk sac component (B). Case 2. Hematoxylin-eosin stain of seminoma, intertubular pattern, involving bilateral testes at low power (C) and high power (D) (original magnifications ×4 [B and C] and ×20 [D]).*

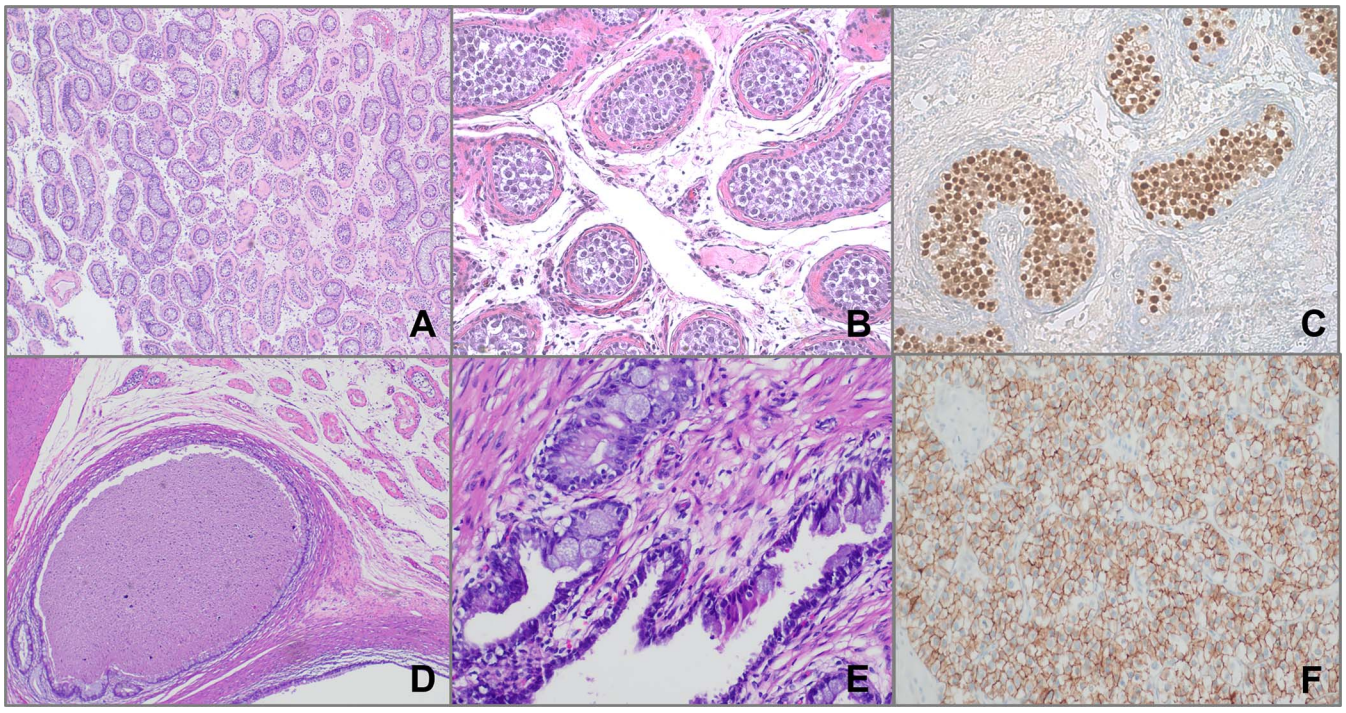

Figure 3. *Case 3. Hematoxylin-eosin stain of germ cell neoplasia in situ at low power (A) and high power (B). Oct-4 immunostaining of germ cell neoplasia in situ (C). Case 4. Hematoxylin-eosin stain of teratoma at high power (D) and low power (E). CD117 immunostaining of seminoma component of the same case (F) (original magnifications ×4 [A and E] and ×20 [B through D and F]).*

The incidence rate at our institution was calculated at 159 per 100 000 per year. The calculated SIR is 26.5 (95% CI, 22.61–30.87), approximately 27 times higher than that previously reported by the National Cancer Institute for the general population.[2] Interestingly, FISH tests were negative for i(12p) among 4 of 5 neoplasms (80%), which was also confirmed by CMA for the cases of bilateral seminoma and seminoma in situ.

DISCUSSION

The higher incidence rate of testicular cancer among transgender females in our series may be due in part to maturation arrest from pretreatment with hormones or blockers, a known risk factor for testicular cancer. There is evidence to suggest a correlation between exogenous hormones—including environmental exposures and hormone supplementation—and testicular cancer development.[3,6,17,26,27] This may arise from endocrine disruption of primordial germ cells and the resulting aberration of development.[26,28,29] This phenomenon is observed in transitioning patients as a result of prolonged pretreatment with hormonal therapy and could potentially explain why study subjects have increased susceptibility to tumorigenesis. In this study, an overwhelming majority of specimens, specifically more than 98%, exhibited changes that are typical of feminizing hormone therapy. These notably include decreased testicular size and weight, maturation arrest, germ cell loss, and interstitial fibrosis. These findings, demonstrated in Figure 1, C and D, are well supported by the current literature on exogenous hormone therapy, and are thought to be due to disruptions in the normal endocrine balance and mechanisms regulating testicular function.

However, despite these prevalent observations aligning closely with existing research, this study challenges previous assertions that there is no link between testicular cancer and hormone therapy.[3] It does so by highlighting the inadequacies in prior research methodologies. Unlike other studies in which patients underwent surgery after only 12 months of hormone therapy, our investigation identified cancer in individuals on GAHT for more than 2 years. This suggests a potential heightened risk associated with prolonged hormone exposure.[3] Additionally, previous studies failed to use

Table 1. Summary of Incidental Testicular Neoplasm Cases, With Details on Age, Hormone Therapy, Histology, Stage, and Follow-up

Case	Age at Orchiectomy, y	Hormonal Therapy, Type and Duration Prior to Orchiectomy	Pathology	Primary Tumor Stage	Follow-up, mo
1	29	Estradiol, spironolactone, 2 y	Embryonal carcinoma with minor yolk sac component	pT2	12 (DF)
2	36	Estradiol, 4 y	Bilateral seminoma, intertubular type	mpT1	6 (DF)
3	26	Estradiol and progesterone, 2.5 y	Germ cell neoplasia in situ	pTis	6 (DF)
4	25	Estradiol and progesterone, 2 y	Teratoma with minor seminoma component	pT1	8 (DF)

Abbreviation: DF, disease free.

Table 2. Summary of Gross, Microscopic, and Molecular Characteristics of Incidental Testicular Neoplasms						
Case	Tumor Size, cm	Blocks per Specimen	Tumor Localization	Components	Additional Findings	Isochromosome 12p
1	1.3 × 1.0 × 0.8	24	Confined to testis	95% embryonal, 5% yolk sac	Germ cell neoplasia in situ Hormone treatment effect	No
2	Not specified	10	Testis A: invades rete testis Testis B: confined to testis	100% seminoma	Germ cell neoplasia in situ Hormone treatment effect	No
3	0.5 × 0.5 × 0.4	8	Confined to testis	100% seminoma	Hormone treatment effect	No
4	1.3 × 0.9 × 0.7	7	Confined to testis	90% teratoma, 10% seminoma	Germ cell neoplasia in situ Hormone treatment effect	Yes

standardized protocol for grossing specimens from gender-affirming orchiectomies—raising concerns about the reliability of their findings.[3] Furthermore, the elevated incidence of testicular cancer in our study (compared with the national average) prompts reevaluation of epidemiologic trends in the United States or the possibility of a localized higher incidence of testicular cancer within our specific microenvironment of geographic location.

CONCLUSIONS

It is possible that the etiology of GCTs in transgender females is distinct from that of the general population. The relatively lower frequency of isochromosome 12p suggests an alternate mechanism could drive tumor development in this population. Further studies are needed to identify the underlying genetics of tumorigenesis.

Understanding the relationship between hormone therapy and testicular cancer becomes imperative with the increasing number of orchiectomy specimens received for gender confirmation surgery. Establishing standardized gross and histologic examination procedures is crucial for informed clinical follow-up, minimizing risks in feminization therapy. Addressing the historical oversight in transgender patient care, these measures aim to enhance clinical practices.

Implications for patient care encompass heightened provider awareness of elevated testicular cancer risk in the transgender population, prompting more frequent screenings for timely intervention. Additionally, this insight may influence pathology guidelines for gender-affirming procedure specimens. Ultimately, these findings advocate for tailored research and improved medical attention to meet the distinctive needs and risks associated with gender-affirming procedures, thus elevating care standards for this population.

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