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LETTER TO THE EDITOR

Male Health

Associations of preorchiectomy hormone levels to testicular germ cell tumor pathology, clinical stage, and size

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Dear Editor,

Despite the substantial body of evidence describing the alternations in and impact of hormones after treatment of unilateral testicular germ cell tumors (GCTs), only a few studies have examined hormone levels before radical orchiectomy.[1] This letter details our investigation of the relationship between preorchiectomy hormone levels and surgical pathology, clinical stage, and tumor size among patients with GCTs. Differences in GCT presentation were expected based on varying preorchiectomy hormone levels.

Clinical and pathological data on testicular cancer patients from January 2013 to November 2018 at the Johns Hopkins Hospital (Baltimore, MD, USA) with available hormone levels prior to orchiectomy, including a full testosterone panel (total testosterone, free testosterone, bioavailable testosterone, and serum hormone-binding globulin), luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and human chorionic gonadotropin (hCG), were collected and used in multivariable statistical analyses. Informed consent to collect data was received from all patients as required by the Institutional Review Board (IRB) of Johns Hopkins Hospital approval process (approval No. IRB00036920). Testicular GCTs were categorized based on surgical pathology into two groups as (pure) seminomas and nonseminomas. Patients were excluded if they were missing any of the above-listed hormones prior to orchiectomy especially estradiol, had a prior orchiectomy, unavailable pathology reports for review, or if they had received prior cytotoxic or chemotherapeutic treatment for oncological reasons. Hormone and tumor size thresholds were set based on the American Urology Association (AUA) guidelines.

Fifty-two patients were identified meeting inclusion criteria. Overall, 80.4% of men were white, with a median age of 31 years. Patients with histories of cryptorchidism (5.8%) and prior testosterone therapy (9.6%) had normal hormone levels at baseline and, therefore, were not excluded. Orchiectomy laterality was 57.7% right; of note, three patients with bilateral tumor involvement had normal preorchiectomy hormone levels. Pure seminoma was present in 48.1% of tumors. Clinical stage was I, II, and III in 73.1%, 17.3%, and 9.6% of patients, respectively. Tumors were <3 cm in 46.2% of patients.

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Based on analyses of categorical hormone levels, elevated preorchiectomy estradiol was significantly associated with nonseminomatous pathology ($P = 0.011$; **Table 1**). Nonseminomas also had a significantly higher median estradiol level compared to seminomas (47.5 pg ml^{-1} *vs* 28.5 pg ml^{-1}, $P = 0.007$). Of note, body mass index (BMI) was not significantly associated with estradiol in our cohort ($P = 0.4$). In logistic regression modeling, when compared to normal estradiol levels, odds of having a nonseminoma were significantly higher in patients with elevated preorchiectomy estradiol (odds ratio [OR] = 16, 95% confidence interval [CI]: 1.6–55.8, $P = 0.017$), even after adjusting for BMI. In addition, elevated preorchiectomy hCG was significantly associated with nonseminomas ($P = 0.010$; **Table 1**), elevated preorchiectomy estradiol ($P = 0.03$), low FSH ($P < 0.001$), and low LH ($P < 0.001$). Importantly, odds of having a nonseminoma remained higher in patients with elevated estradiol while accounting for hCG (OR = 10.5, 95% CI: 1.2–75.6, $P = 0.041$). Further analyses revealed no significant associations between hormones and clinical stage ($P = 0.104$ and 0.082 for estradiol and total testosterone, respectively). Finally, elevated preorchiectomy LH and FSH levels were significantly associated with larger tumor size compared to normal levels (median size of 7.7 cm *vs* 3.5 cm for LH, $P = 0.047$; 6.1 cm *vs* 2.9 cm for FSH, $P = 0.018$).

Our aim was to determine the association between preorchiectomy hormone levels and surgical tumor pathology, clinical stage, and testis mass size among a representative population of men presenting with testicular GCTs. Interestingly, elevated estradiol levels were significantly associated with nonseminomatous pathology regardless of BMI and hCG levels, and elevated hCG levels were also significantly associated with nonseminomas. To date, only a few studies have examined similar preorchiectomy hormone level associations to GCT pathology. Wiechno *et al*.[1] similarly observed estradiol being a significant marker of nonseminomatous GCTs. It has been proposed that disruptions in the pituitary-gonadal axis among men with GCTs may be due to either high hCG concentrations produced or high estradiol secreted directly by tumor due to hCG.[2,3] Our data demonstrate that nonseminomas are associated with not only elevated estradiol but also hCG, supporting arguments of both hCG-influenced production of estradiol and overall disruptions in the pituitary-gonadal axis. Nakazumi *et al*.[4] also described significantly elevated estradiol and hCG in patients with nonseminomas compared to seminomas. Our evidence corroborates these recent studies that have shown elevations in estradiol are

Table 1: Distribution of surgical pathology based on preorchiectomy hormone levels in patients who underwent radical orchiectomy for testicular germ cell tumors

Hormone level	Seminoma	Nonseminoma	P
Total testosterone (ng dl⁻¹)			
Median (IQR)	403 (327–550)	555 (280–869)	0.188
Low (<300), n (%)	4 (36.4)	7 (63.6)	0.229
Normal (300–1100), n (%)	19 (57.6)	14 (42.4)	
High (>1100), n (%)	0 (0)	3 (100)	
Luteinizing hormone (mIU ml⁻¹)			
Median (IQR)	4.9 (2.8–8.8)	3.7 (0.8–8.7)	0.169
Low (<1.7), n (%)	2 (28.6)	5 (71.4)	0.253
Normal (1.7–11.2), n (%)	15 (62.5)	9 (37.5)	
High (>11.2), n (%)	1 (33.3)	2 (66.7)	
Follicle-stimulating hormone (mIU ml⁻¹)			
Median (IQR)	4.8 (3.1–14.8)	2.1 (0.3-6.2)	0.075
Low (<1.5), n (%)	2 (33.3)	4 (66.7)	0.423
Normal (1.5–7.6), n (%)	10 (58.8)	7 (41.2)	
High (>7.6), n (%)	6 (66.7)	3 (33.3)	
Estradiol (pg ml⁻¹)			
Median (IQR)	28.5 (22.7–33.5)	47.5 (36.1–67.9)	0.007*
Normal (0–50), n (%)	16 (69.6)	7 (30.4)	0.011*
High (>50), n (%)	1 (12.5)	7 (87.5)	
Human chorionic gonadotropin (mIU ml⁻¹)			
Median (IQR)	0.9 (0.9–2.2)	16 (0.9–55)	0.149
Normal (0–3), n (%)	18 (64.3)	10 (35.7)	0.010*
High (>3), n (%)	5 (25.0)	15 (75.0)	

*$P<0.05$. IQR: interquartile range

associated more with nonseminomatous pathology, even though both nonseminomas and seminomas can produce hCG, by accounting for hCG in estradiol analyses. Further work with immunohistochemistry has revealed increased estrogen receptor β-subtype expression among nonseminomas, specifically endodermal sinus tumors and teratomas.[5,6] Overall, in addition to our study, prior work suggests that estradiol itself may increase risk for GCTs in addition to the influences of hCG production and specific estrogen receptors on nonseminomatous GCTs.

This study additionally observed a significant association between elevated preorchiectomy levels of LH and FSH and larger GCTs. Although the mechanism was not explored in this study, we propose this association is explained by larger tumors disrupting surrounding parenchyma, leading to impaired spermatogenesis and positive feedback increase in LH and FSH.[7] Similar elevations in LH and FSH have been observed after chemotherapy and orchiectomy, which lead to loss of tissue in one or both testes.[8,9] Prior investigations have also suggested that impaired spermatogenesis in nonseminomas compared to seminomas may be caused by increased tumor size in addition to a potential influence of increased aromatization of testosterone to estradiol.[4] Bandak et al.[10] similarly observed greater odds of Leydig cell dysfunction with increasing tumor size. Based on our study and prior work, observed elevations in LH and FSH among larger GCTs may be due to a combination of positive feedback from disruption of normal testis parenchyma, impaired spermatogenesis, and elevated estradiol levels present.

Our study has several limitations that merit discussion. The study's retrospective design introduces the possibility of selection bias. Due to our strict inclusion and exclusion criteria, only 52 patients had all required preorchiectomy hormone levels including estradiol prior to orchiectomy. Moreover, hormone levels were not tracked after

orchiectomy, which would allow assessment of hormone alterations over time after surgery. Further longitudinal studies including factors that influence the pituitary-gonadal axis, such as smoking status, activity, and thyroid stimulating hormone, with larger patient cohorts are recommended to help mitigate these limitations and provide additional evidence of important relationships between preorchiectomy hormone levels and GCTs characteristics.

In conclusion, among patients presenting with GCTs, elevated preorchiectomy estradiol appears to be predictive of nonseminomatous pathology, while elevated preorchiectomy LH and FSH are associated with larger tumor size.

AUTHOR CONTRIBUTIONS

COMPETING INTERESTS

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