



Germ Cell Neoplasia in Situ of the Testis and Azoospermia: Case Report and Review of the Literature

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Abstract

An increased risk of testicular cancer in men with infertility and poor semen quality has been reported. We aim to present a patient who was being studied for infertility and incidentally found a testicular nodule, discuss management and prevalence of small testicular masses.

Keywords

Germ Cell Neoplasia in Situ, Azoospermia, Infertility, Small Testicular Masses, Case Report

Abbreviations

GCNIS: Germ Cell Neoplasia in Situ; STMs: Small Testicular Masses; US: Ultrasound; NOA: Non-Obstructive Azoospermia

Introduction

Historically testicular masses have presented as palpable lesions but scrotal Ultrasound (US) has rapidly become the preferred modality to detect scrotal pathology with sensitivity approaching 100% for testicular masses [1,2]. Now with increasing use and availability of US technology, we are seeing an increase in incidental masses in other organs such as the testes and we are faced with the question of how to act upon these findings without compromising patient care [3,4]. The current literature on long-term follow-up and safety data on nonpalpable small testicular masses (STMs) is lacking [5].

The prevalence of germ cell neoplasia in situ (GCNIS) is increased in non-obstructive azoospermia

(NOA) [6] and increases with the degree of spermatogenic impairment [7]. GCNIS is a precursor lesion that eventually becomes malignant [8].

Histologic evaluation of the testicular biopsy is considered the gold standard for diagnosis of GCNIS [9]. Additional use of the immunohistochemical tumor markers PLAP and OCT 3/4 enhances the accuracy of histologic evaluation [10,11]. However, when only a standard testicular biopsy (3x3 mm) is performed, a false-negative result is possible due to the focal distribution of GCNIS [12,13].

Case Presentation

A 42-year-old male patient presented with secondary infertility. Physical exam was unremarkable.

Case Report

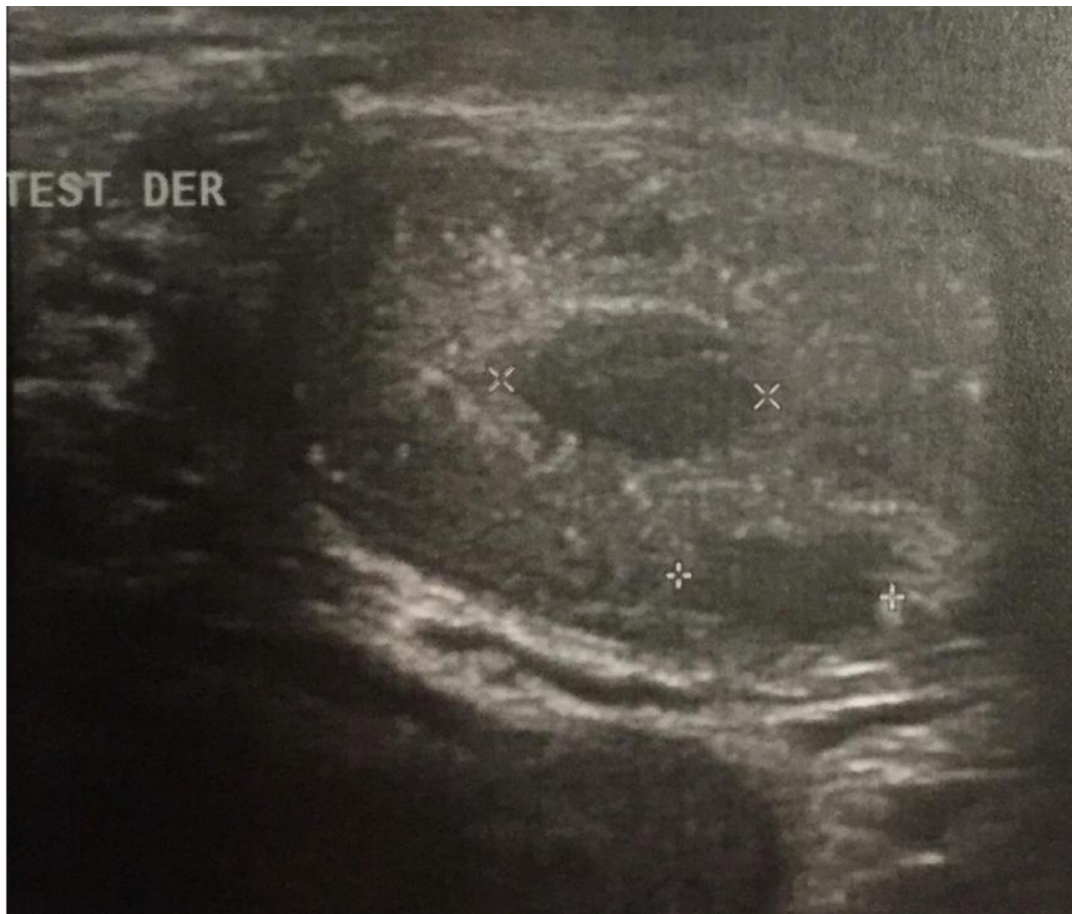


Fig-1: Ultrasound

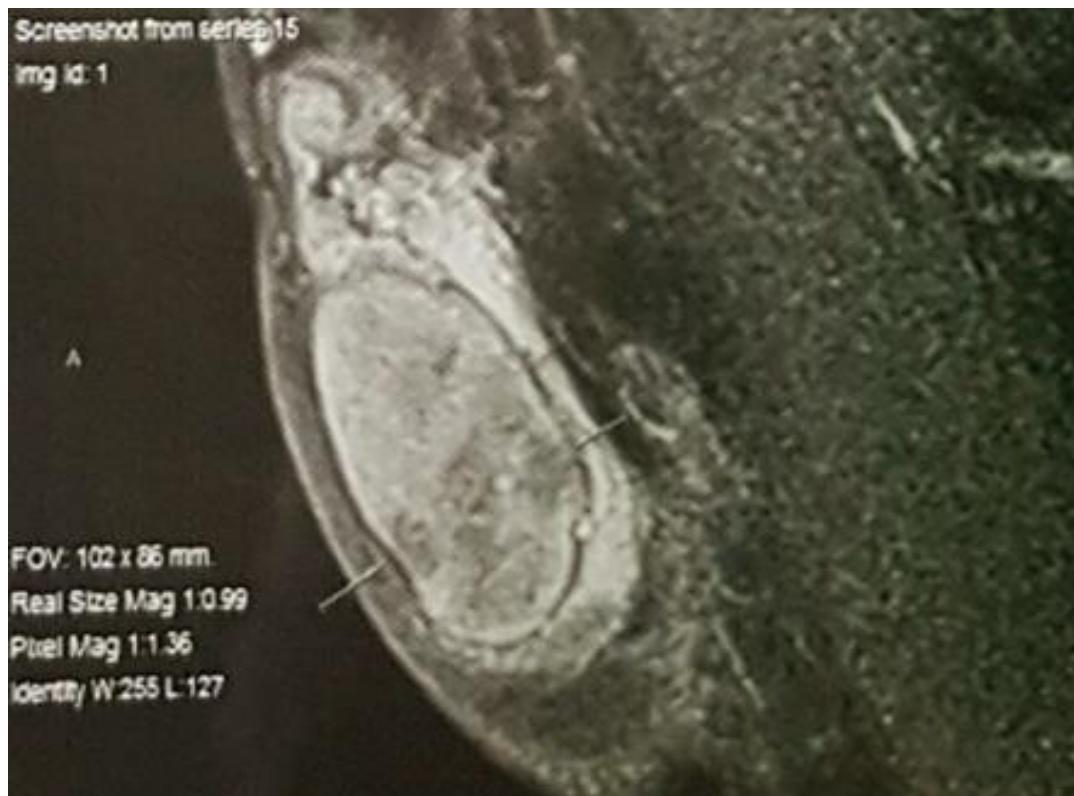


Fig-2: Magnetic Resonance

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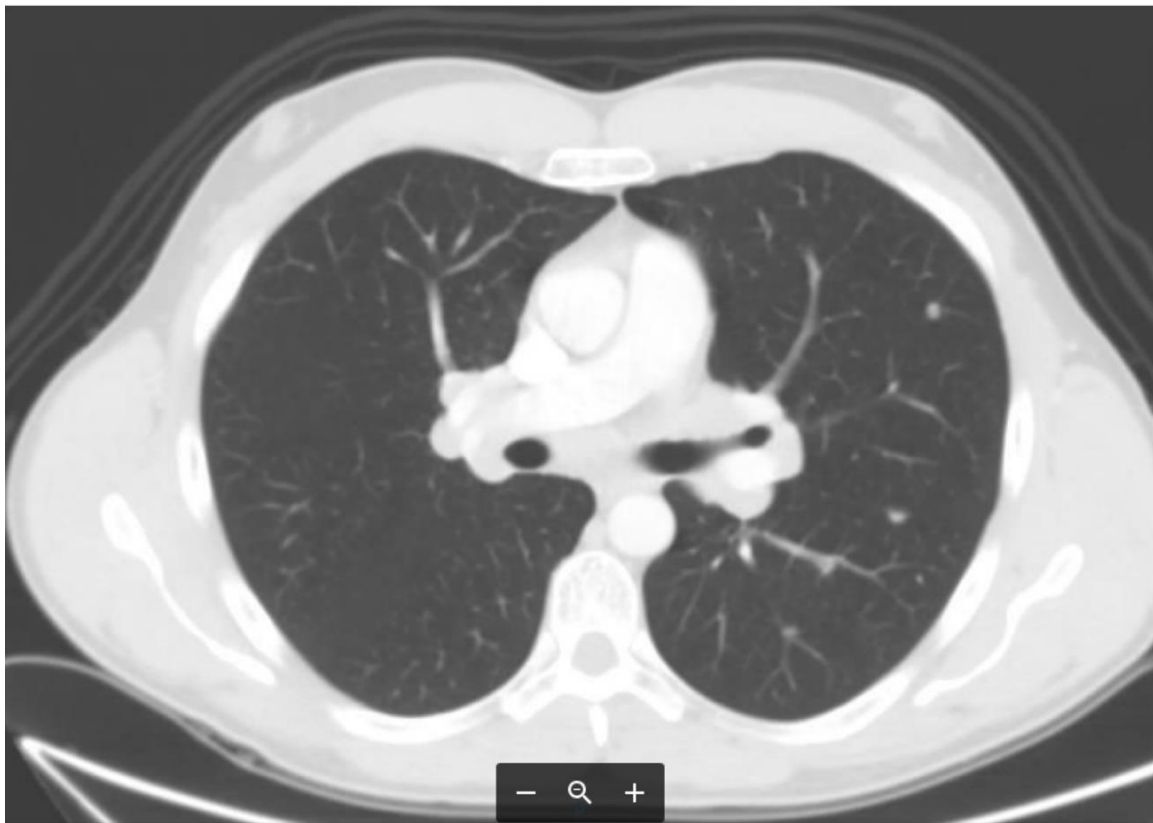
US showed right testis with multiple calcifications and hypoechogenic oval images with poor vascular peripheral signal measuring 6 to 8 mm (**Fig-1**). Spermogram showed NOA. Laboratory workup revealed normal tumor markers. He was submitted to a Magnetic resonance (MR) that showed in lower pole of the right testis pseudonodular images without contrast enhancing (**Fig-2**).

The patient was scheduled for testicular sperm extraction (TESE) and biopsy of lower pole. Intraoperative biopsy showed azoospermia and seminoma. Therefore, he underwent right orchiectomy (**Fig-3**). The postoperative period was uneventful and the patient exited the hospital the next day.

Histopathological evaluation of the specimens revealed GCNIS. Tumor cells stained positive for OCT $3/4$. Chest abdomen pelvis Computed Tomography (CT) scan showed multiple nodules smaller than 5 mm and mediastinal lymph nodes (**Fig-4**). Biopsy of mediastinal lymph nodes revealed Sarcoidosis.



Fig-3: Right orchiectomy



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Fig-4: Chest abdomen pelvis Computed Tomography (CT) scan

Discussion

Infertility and testicular cancer have been linked, with germ cell tumors found in up to 0.5% of men with infertility, a nearly 20-fold greater prevalence than in the general population [14,15]. Classic teaching about the treatment of solid testicular lesions is extirpative surgery with radical orchiectomy due to the risk of germ cell tumor [5]. However, this dogma is changing as experience has demonstrated that many incidentally discovered small masses prove to be benign [5]. Bieniek et al., reported 120 infertile men that were diagnosed with incidental sub centimeter hypoechoic testicular masses. Average follow up was 1.3 years and 18 men underwent surgical exploration. Malignant seminoma was found in 6 patients, comprising 5% of the overall cohort [5]. Eifler et al., discovered 49 testicular abnormalities, including 20 that were hypoechoic, in a total of 145 men undergoing scrotal US to evaluate non-obstructive azoospermia [16]. At sperm retrieval 14 men with hypoechoic masses 1 cm or less underwent excision and all showed benign pathology.

Novel biomarkers and imaging techniques may eventually help define the malignant risk in men found to have incidental STMs (Fig-5) [5] Routine staging CT

appears unnecessary for these lesions [17]. A high number of non-palpable testicular nodules may be found by the combined use of testicular ultrasound and biopsy in azoospermic men examined for infertility [7]. Mancini et al., evaluated 145 azoospermic patients. Testicular ultrasonographic nodules were found in 11 out of 145 patients (7.5%). Ninety-seven, including the 11 with testicular nodules, were asked to submit to TESE and biopsy to search for spermatozoa. Nine out of the 11 subjects with testicular nodules underwent a more extensive microsurgical exploration and they found one seminoma, one embryonal carcinoma, three Leydig cell tumours and four Leydig hyperplasias. The biopsies which were routinely performed during TESE detect two additional GCNIS [7]. In azoospermic patients TESE must be accompanied by anatomopathological study, not only for define the cause of infertility but to discard also associated serious diseases, such as tumors of germ cells and GCNIS [18].

Conclusion

Small, nonpalpable, hypoechoic lesions with negative tumor markers detected incidentally during evaluation for infertility can be safely follow up with serial ultrasound. Before TESE, in azoospermic

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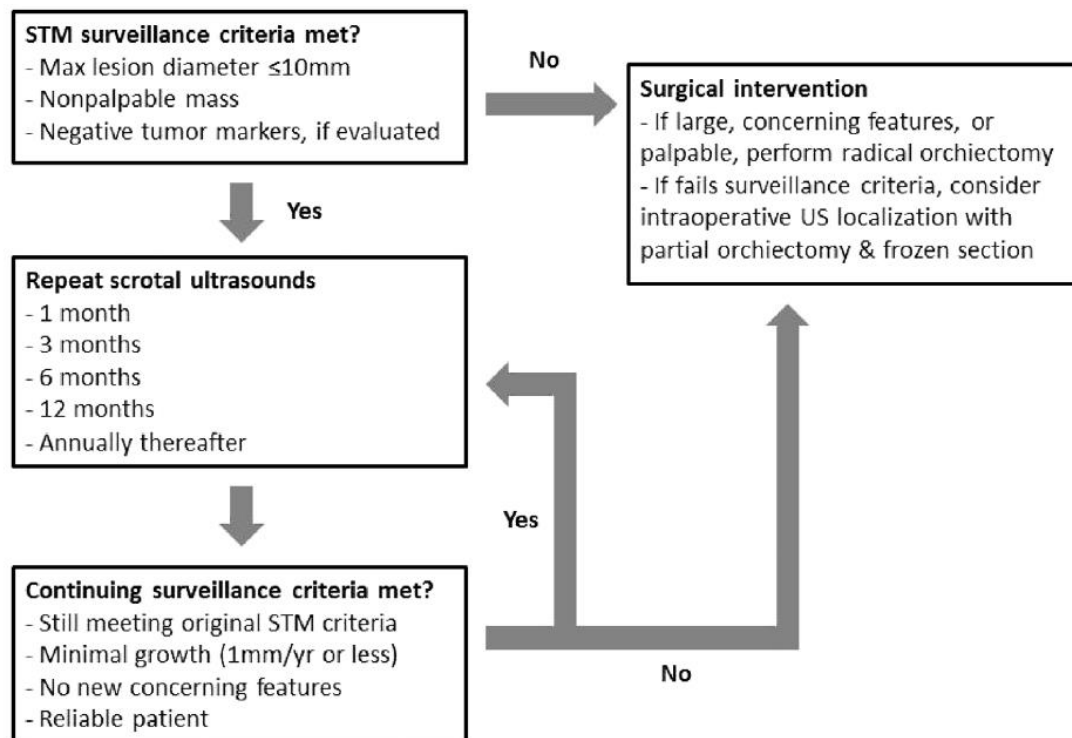


Fig-5: Suggested small testicular mass surveillance algorithm

patients it should be mandatory to submitted the patient to scrotal US based on the high prevalence of non-palpable testicular nodules detected as small cancer upon surgery.

Conflict of Interest

The authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

References

- [1] Appelbaum L, Gaitini D, Dogra VS. Scrotal ultrasound in adults. *Semin Ultrasound CT MR*. 2013 Jun;34(3):257-73. [PMID: 23768892]
- [2] Winter TC. There is a mass in the scrotum-what does it mean?: Evaluation of the scrotal mass. *Ultrasound Q*. 2009 Dec;25(4):195-205. [PMID: 19956052]
- [3] Silverman SG, Israel GM, Herts BR, Richie JP. Management of the incidental renal mass. *Radiology*. 2008 Oct;249(1):16-31. [PMID: 18796665]
- [4] Conti A, Santoni M, Sotte V, Burattini L, Scarpelli M, Cheng L, Lopez-Beltran A, Montironi R, Cascinu S, Muzzonigro G, Lund L. Small renal masses in the era of personalized medicine: Tumor heterogeneity,

growth kinetics, and risk of metastasis. *Urol Oncol*. 2015 Jul;33(7):303-309. [PMID: 25979651]

- [5] Bieniek JM, Juvet T, Margolis M, Grober ED, Lo KC, Jarvi KA. Prevalence and Management of Incidental Small Testicular Masses Discovered on Ultrasonographic Evaluation of Male Infertility. *J Urol*. 2018 Feb;199(2):481-86. [PMID: 28789946]

- [6] Rørth M, Rajpert-De Meyts E, Andersson L, Dieckmann KP, Fosså SD, Grigor KM, Hendry WF, Herr HW, Looijenga LH, Oosterhuis JW, Skakkebaek NE. Carcinoma in situ in the testis. *Scand J Urol Nephrol Suppl*. 2000;(205):166-86. [PMID: 11144894]

- [7] Mancini M, Carmignani L, Gazzano G, Sagone P, Gadda F, Bosari S, Rocco F, Colpi GM. High prevalence of testicular cancer in azoospermic men without spermatogenesis. *Hum Reprod*. 2007 Apr;22(4):1042-46. [PMID: 17220165]

- [8] Dohle GR, Elzanaty S, van Casteren NJ. Testicular biopsy: clinical practice and interpretation. *Asian J Androl*. 2012 Jan;14(1):88-93. [PMID: 22157985]

- [9] Hessel ML, Ramos L, D'Hauwers KW, Braat DD, Hulsbergen-van de Kaa CA. Beneficial value of testicular sperm extraction-AgarCyto in addition to the standard testicular biopsy for diagnosis of testicular germ cell tumors in nonobstructive azoospermia. *Fertil Steril*. 2016 Feb;105(2):308-14.e1. [PMID: 26493121]

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- [10] Dieckmann KP, Kulejewski M, Heinemann V, Loy V. Testicular biopsy for early cancer detection--objectives, technique and controversies. *Int J Androl*. 2011 Aug;34(4 Pt 2):e7-13. [PMID: 21615417]
- [11] van Casteren NJ, de Jong J, Stoop H, Steyerberg EW, de Bekker-Grob EW, Dohle GR, Oosterhuis JW, Looijenga LH. Evaluation of testicular biopsies for carcinoma in situ: immunohistochemistry is mandatory. *Int J Androl*. 2009 Dec;32(6):666-74. [PMID: 18798762]
- [12] van Casteren NJ, Boellaard WP, Dohle GR, Weber RF, Kuizinga MC, Stoop H, Oosterhuis WJ, Looijenga LH. Heterogeneous distribution of ITGCNU in an adult testis: consequences for biopsy-based diagnosis. *Int J Surg Pathol*. 2008 Jan;16(1):21-24. [PMID: 18203779]
- [13] Oosterhuis JW, Stoop H, Dohle G, Boellaard W, van Casteren N, Wolffebuttel K, Looijenga LH. A pathologist's view on the testis biopsy. *Int J Androl*. 2011 Aug;34(4 Pt 2):e14-19; [PMID: 21790650]
- [14] Pierik FH, Dohle GR, van Muiswinkel JM, Vreeburg JT, Weber RF. Is routine scrotal ultrasound advantageous in infertile men? *J Urol*. 1999 Nov;162(5):1618-20. [PMID: 10524881]
- [15] Carmignani L, Bozzini G. Re: Increased incidence of testicular cancer in men presenting with infertility and abnormal semen analysis. J. D. Raman, C. F. Nobert and M. Goldstein. *J Urol*. 2006 Apr;175(4):1574; [PMID: 16516050]
- [16] Eifler JB Jr, King P, Schlegel PN. Incidental testicular lesions found during infertility evaluation are usually benign and may be managed conservatively. *J Urol*. 2008 Jul;180(1):261-64; discussion 265. [PMID: 18499177]
- [17] Toren PJ, Roberts M, Lecker I, Grober ED, Jarvi K, Lo KC. Small incidentally discovered testicular masses in infertile men--is active surveillance the new standard of care? *J Urol*. 2010 Apr;183(4):1373-77. [PMID: 20171671]
- [18] Gomis C, Sarquella J, Arce Y, Vinay JI. Neoplasia intratubular testicular e infertilidad: azoospermia asociada a neoplasia intratubular testicular bilateral [Testicular intraepithelial neoplasia and infertility: Azoospermia associated with bilateral testicular intraepithelial neoplasia]. *Revista Internacional de Andrología*. 2017 Oct 1;15(4):165-68. Spanish.