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# Primary testicular neuroendocrine tumor with azoospermia: Extending indications for testicle-sparing surgery

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## Introduction

Neuroendocrine tumors (NETs), commonly called carcinoid tumors, are extremely rare and accounts for only 0.2% of all carcinoid and testicular neoplasms [1]. NETs can arise from neuroendocrine cells throughout the body, but mostly detected in the gastrointestinal tract and bronchopulmonary system. It can produce peptides that cause characteristic hormonal syndromes and may have an indolent or aggressive course.

The diagnosis of these neoplasms is based mainly on the immunohistochemistry study. They have a good prognosis, with a 5-year overall and specific survival rates of 78.7% and 84.3%, respectively [2]. Whereas radical orchiectomy is the treatment of choice for testicular TETs, the current report will present atypical primary testicular tumor, which has been managed by excision of the testicular mass under ultrasound guidance, using excisional frozen biopsy, followed by orchiopexy. Up to knowledge, this case represents rarity of rarity; presents with primary infertility and managed by testicular preservation.

### *Case presentation*

A 33-year-old man presented with an incidentally-detected right testicular mass during work-up for primary infertility due to azoospermia. No history of diarrhea, hot flashes, palpitations, accompanied dragging pain, fever or any recent travel history outside the country. No history of recent testicular infection or trauma. Clinically, the mass was firm in consistency, not tender, with well-defined edges. The left testis was normal in size and consistency, with impalpable inguinal lymph nodes bilaterally. Laboratory work-up, tumor markers and hormonal profiles were all within normal ranges, including serum alpha-fetoprotein [1.89 IU/mL (< 5.90)], beta-human chorionic gonadotropin [0.10 mIU/mL (< 2.6)], total testosterone [4.43 ng/mL (2.49–8.36)], luteinizing hormone [5.4 mIU/mL (1.7–8.6)], and follicle stimulating hormone [2.24 mIU/mL (1.50–12.20)]. Semen analysis showed azoospermia.

Scrotal sonography revealed normal size, echogenicity and vascularity of the right testis, measuring 4 × 2x3 cm with focal homogenous hypoechoic nodule measuring 1.0 × 0.6 cm with increased vascularity (Fig. 1A&B). Normal left testis, which contains 3-anechoic well-defined tiny simple cysts. Multiple axial computed tomography images of the abdomen and pelvis confirmed the enhancement of the previously described nodule (Fig. 2A), with no evidence of abdominal or pelvic lymphadenopathy apart from a small portacaval lymph node measured 6-mm. Contrast-enhanced MRI of the testes showed a well-defined lobulated intra-testicular soft tissue mass lesion measuring 10-mm in diameter, displaying T2 hypointensity with no extra-testicular exten-

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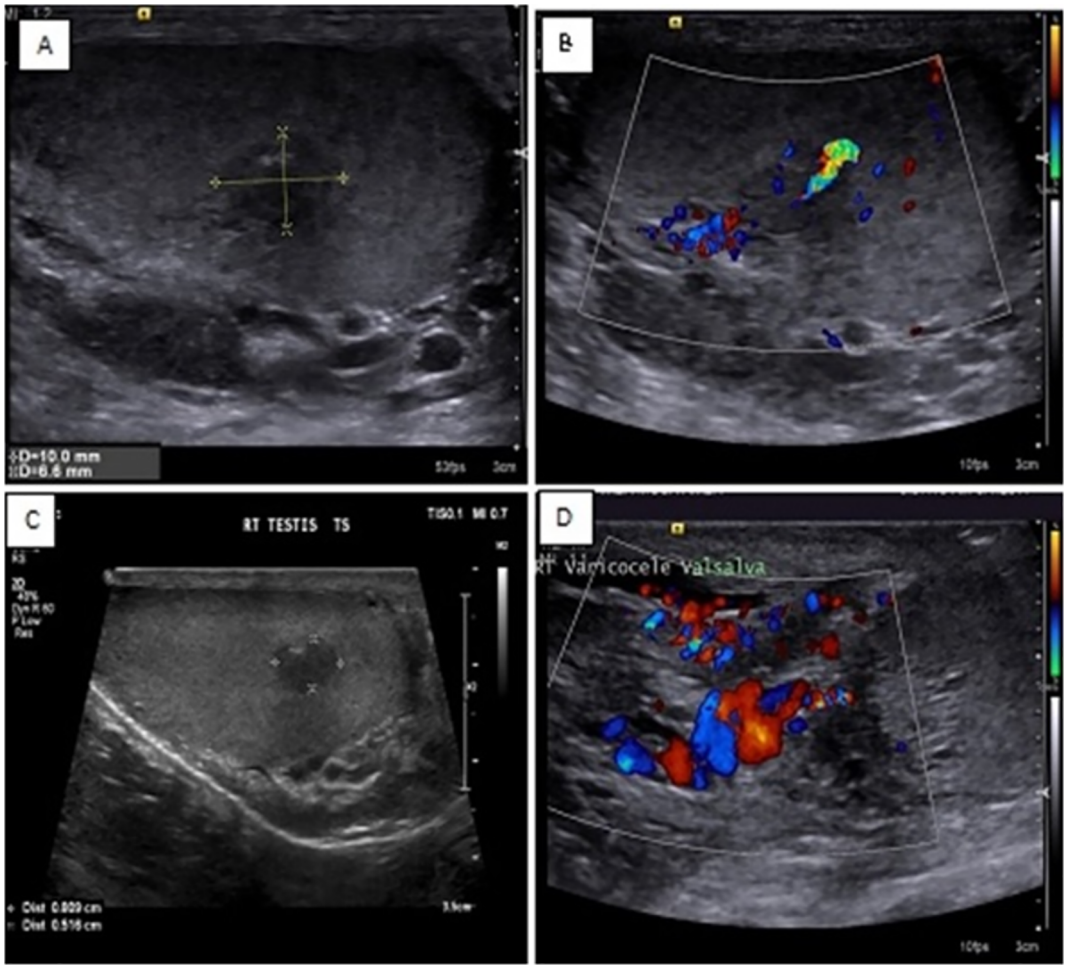


**Fig. 1.** Scrotal sonography at first presentation (A &B) showed normal size, echogenicity and vascularity of the right testis, measuring 4 × 2x3 cm with focal homogenous hypoechoic nodule measuring 10 × 6 mm with increased vascularity. Follow-up scrotal sonography after one-year (C &D) showed normal size, echogenicity and vascularity of the right testis, with focal homogenous hypoechoic nodule measuring 8.5 × 5x8 mm with increased vascularity.

sion (Fig. 2B&C). Patient refused surgery at that time and did not show-up for 12-months before coming back for re-evaluation of his primary infertility. Clinically, there was not any gross change in the right testicular mass parameters, while semen analysis showed persistence of azoospermia. Follow-up scrotal ultrasonography was consistent with that previously performed, with mild degree varicocele detected on Valsalva (Fig. 1C&D).

Right inguinal exploration was performed for focal excision of the testicular mass under ultrasound guidance. Excisional frozen biopsy showed no malignancy, followed by right orchiopexy with uneventful postoperative course. Properly controlled immune-histochemical stains showed positive CKAE1/AE3, synaptophysin, and Chromogranin in tumor cells, all of which are markers for NETs. Ki-67 was 0%, while CD-56, inhibin, and CD-99 were negative in tumor cells, further excluding other possible germ cell tumors. Therefore, morphological features and immunohistochemical profiles were consistent with a well-differentiated NET (GI), and the tumor margin was negative for tumor with no anaplasia, necrosis, or mitoses (Fig. 3).

Background testicular tissue sowed thickened basement membrane and Sertoli cells only seen in some of the tubules, features favoring atrophic tubules. Some tubules showed arrested maturation on stage of spermatocytes and spermatids. The patient underwent regular and strict follow-up with abdominal computed tomography and scrotal sonography, and no evidence of tumor recurrence detected.

## Discussion

Primary testicular NET is extremely rare, and the diagnosis is based on the immunohistochemistry study. It has good prognosis, especially for localized carcinoid tumors after resection. Adjuvant radiotherapy or chemotherapy for advanced disease shows only minimal benefits. The current index case was diagnosed during the work-up of an infertile man with azoospermia by ultrasonography, while computed tomography and MRI confirmed the primary nature of the tumor. There was no carcinoid syndrome, including diarrhea, hot flashes, and palpitations, consistent with rarity of this syndrome.

Testicular NET seems still to have its own secrets with wide diversity in presentation and management. A recent case of primary

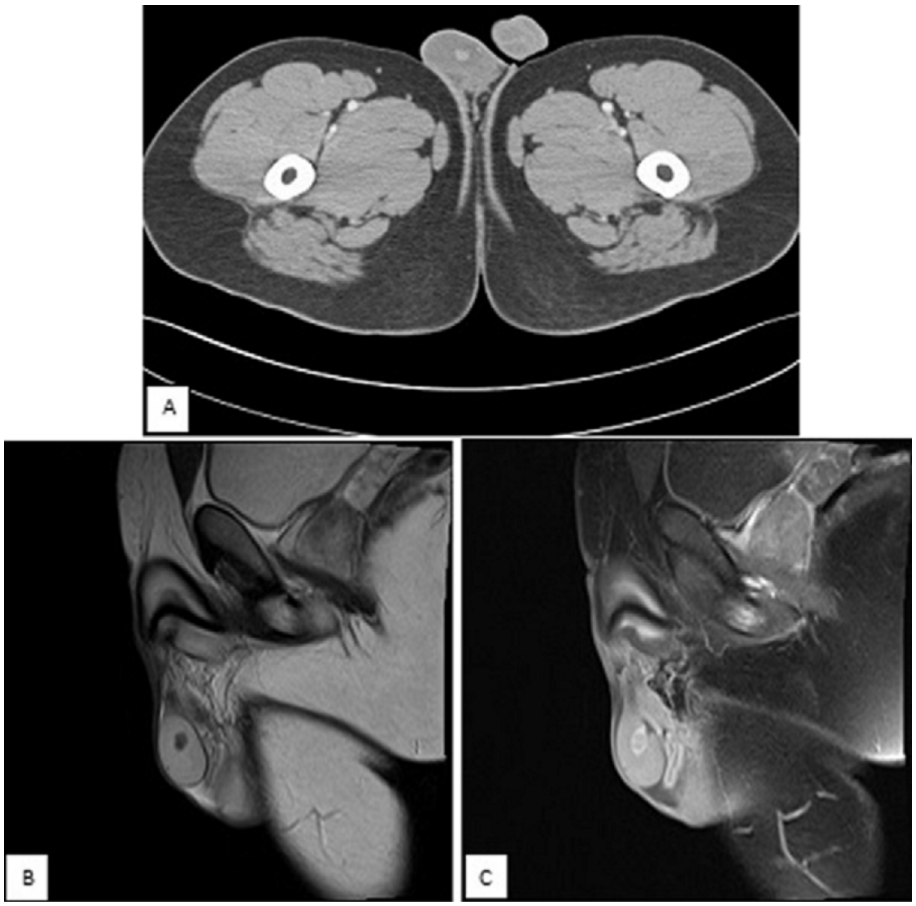


**Fig. 2.** Multiple axial computed tomography after intravenous contrast injection (A) confirmed the enhancement of the right testicular nodule. Contrast-enhanced MRI of the testes (B &C) showed a well-defined lobulated intra-testicular soft tissue mass lesion measuring 10-mm in diameter, displaying T2 hypointensity and post-contrast avid enhancement, with no extra-testicular extension.

bilateral synchronous testicular carcinoid tumor was treated with a bilateral testicular-sparing surgery [3]. Due to the primary infertility and localization of the small mass, a testicular-preserving approach was planned. Focal excision of the testicular mass under ultrasound guidance was performed, while excisional frozen biopsy showed no malignancy, followed by right orchiopexy. All intratesticular masses were virtually treated with radical orchiectomy until a short time ago. However, testicle-sparing surgery is currently recommended for bilateral and/or multiple lesions or in monorchid patients. This index case extends indications for testicle-sparing surgery to include primary infertility. This would improve the fertility, endocrine function, cosmetic effects and patient's quality of life. Despite it is not a usual procedure in testicular tumor surgery, frozen section done in this index case was indispensable to exclude the presence of malignancy and confirm negative resection margins of the tumor, after considering the clinical data, tumor markers, and ultrasonographic findings.

Lack of mitotic figures in this index case was consistent with the previously revised 29 NETs with rare mitotic figures, detected in only three cases [4]. Therefore, most typical primary testicular carcinoid tumors have a benign clinical course with favorable prognosis and do not exhibit metastatic spread. However, histologic grade can influence the long-term prognosis, where cases with typical histology did not show recurrence or metastases after 53-months follow-up, while 25% of patients with atypical histology did metastasized [4]. Metastases reported to occur up to 17-years after the initial treatment [5], indicating the need for regular long-term follow-up. However, the follow-up strategy of testicular carcinoid after surgical resection is a matter of debate and the available data is sparse to conclude a well-defined protocol.

## Conclusion

The current index case extends the indication for-testicle-sparing surgery to include primary infertility, especially with localized small masses. Intraoperative frozen section seems to be indispensable to confirm negative resection margins of the tumor, after considering the clinical data, tumor markers, and ultrasonographic findings.

## Disclosure statement

No competing financial interests exist.

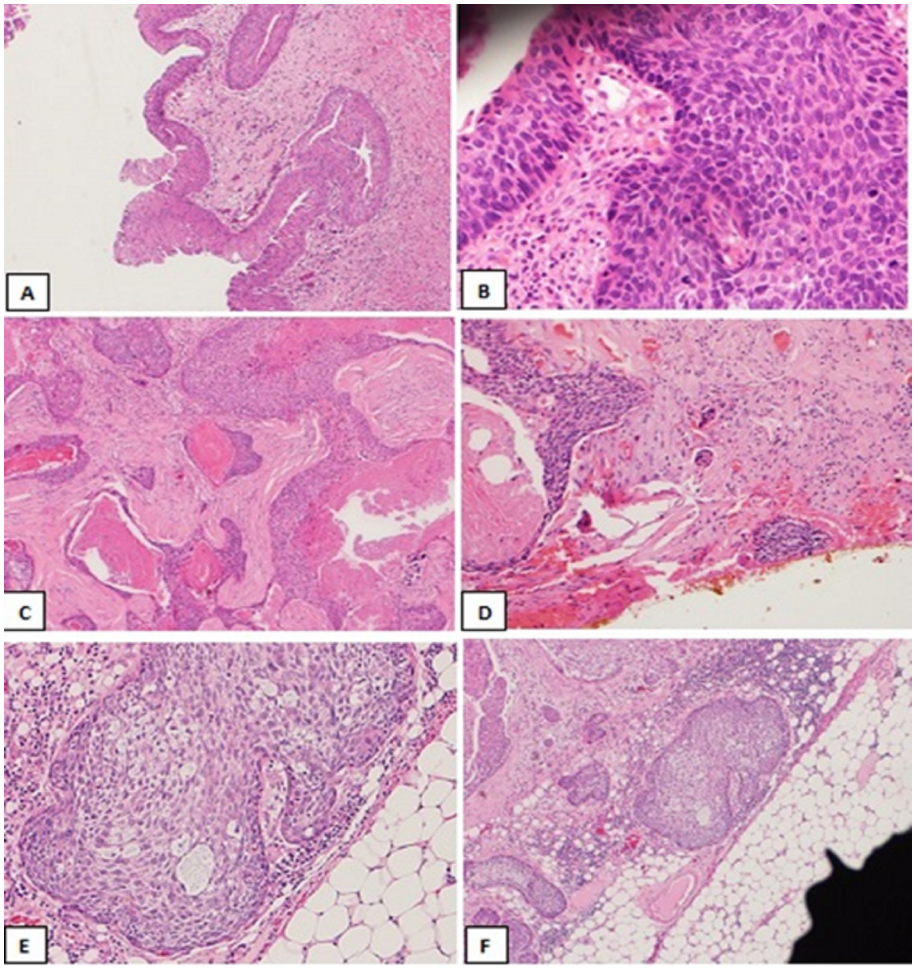


**Fig. 3.** Low power histopathological image (4x) showing seminiferous tubules of testis with tumor present in nests and tubular configuration in between in fibrous stroma [A]. High power image (20x) showing tumor nests and tubules with intraluminal calcifications also noted [B]. High power (40x) image showing granular eosinophilic cytoplasm and rounded nuclei with salt and pepper chromatin [C]. Chromogranin positive neuroendocrine cells [D].

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