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HISTOPATHOLOGY INSIGHTS, MOLECULAR CORRELATES, AND CLINICAL IMPLICATIONS OF NEUROENDOCRINE CARCINOMA OF THE TESTIS: A CASE REPORT.

PERSPECTIVAS HISTOPATOLÓGICAS, CORRELACIONES MOLECULARES E IMPLICACIONES CLÍNICAS DEL CARCINOMA NEUROENDOCRINO DEL TESTÍCULO: REPORTE DE UN CASO.

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RESUMEN
Neoplasias neuroendocrinas testiculares representan un subconjunto extremadamente raro de malignidades genitourinarias, constituyendo menos del 1% de todas las neoplasias testiculares. Pueden aparecer en un amplio rango de edad y surgir como lesiones testiculares primarias o como enfermedad metastásica, con mayor frecuencia desde el tracto gastrointestinal. Su rareza y presentación diversa suelen causar retrasos diagnósticos, especialmente cuando no hay síndromes clínicos u hormonales clásicos. Presentamos el caso de una NEN testicular manifestada como una masa testicular unilateral en un hombre adulto.

ABSTRACT
Testicular Neuroendocrine neoplasms represent an exceedingly rare subset of genitourinary malignancies accounting for <1% of all testicular neoplasms. They occur across a wide age range and may arise as primary testicular lesions or metastatic disease, most frequently from the gastrointestinal tract. Their rarity and diverse presentation often lead to diagnostic delays, especially in settings where classic clinical or hormonal syndromes are absent. We report a case of a testicular NEN presenting as a unilateral testicular mass in an adult male.

Keywords: Testicular Neuroendocrine Neoplasm (TNEN), Neuroendocrine Neoplasm (NEN) Neuroendocrine Tumor (NET), Neuroendocrine Carcinoma (NEC), Germ-cell tumor (GCT), germ cell neoplasia in situ (GCNIS).
Palabras clave: Neoplasia neuroendocrina testicular (TNEN), neoplasia neuroendocrina (NEN), tumor neuroendocrino (NET), carcinoma neuroendocrino (NEC), tumor de células germinales (GCT), neoplasia de células germinales in situ (GCNIS).

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INTRODUCTION

TNEN's are a rare group of non GCNIS related germ cell tumors accounting for less than 1% of all gonadal neoplasms[1]. Historically, Primary TNEN's were grouped under the term "well differentiated neuroendocrine tumor" or Carcinoids[2]. These lesions are now subclassified by the WHO 2022 framework into prepubertal NETs and postpubertal NECs[2,3]. Prepubertal neuroendocrine tumors are often benign, seen in association with Teratomasin about 25% of cases and exhibit good prognosis following excision[1]. NECs typically manifest an aggressive clinical course analogous to extrapulmonary NECs, with rapid progression and early dissemination[4]. Where TNEN's occur in the absence of associated gonadal neoplasms, they are referred to as "pure". Because they may mimic germ cell tumors (GCTs), lymphomas, or metastatic small cell carcinoma, accurate identification is critical[5]. The rarity of testicular NENs necessitates a pathology centered integration of current data to inform diagnosis, classification, and clinical management.

The pathogenesis of testicular NENs remains incompletely understood. Proposed mechanisms include: de novo origin from neuroendocrine cells within the testicular parenchyma or rete testis; somatic-type malignant transformation of a teratomatous element within a GCNIS-related germ cell tumor; and metastatic implantation from extra-testicular primaries, particularly lung or gastrointestinal tract[6,7]. Molecular evidence suggests shared pathways with systemic NECs, including p53 and RB1 alterations, and loss of heterozygosity at chromosome 3p compared with isochromosome 12p or numerical aberrations in the X chromosome, which are more commonly seen in GCNIS derived germ cell tumors[2]. Somatic-type transformation within a Teratoma often displays divergent differentiation—sarcomatous, glandular, or neuroendocrine—driven by clonal evolution within residual teratomatous foci[6]. Thus, comprehensive morphologic and immunohistochemical assessment remains the cornerstone for determining origin.

Patients usually present with a painless, unilateral testicular mass; systemic carcinoid symptoms such as flushing or diarrhea are rare [7–9]. Serum tumor markers (AFP, β-hCG, LDH) are typically normal, helping to distinguish NECs from mixed GCTs[1]. Some writers have reported azoospermia as an association with a "carcinoid" tumor of the testis[10]. And while hydroceles and cryptorchidism have been reported by some writers, these are not a common findings in TNEN's[7]. A single case of Ovotestis NEC has been reported in a female patient[11].

Scrotal ultrasonography is the main imaging technique utilized for the assessment of the scrotal contents and in some cases reveals a solid, hypoechoic intratesticular mass, occasionally with necrosis or calcifications[12].Reporting of sonographic findings in the various case series however is heterogeneous and the reported features often overlap with other testicular neoplasms and across the NET/NEC categories.[12]. Cross-sectional imaging—contrast-enhanced CT, MRI are useful in assessing retroperitoneal and distant spread while Positron emission tomography (PET/CT) is useful in the detection of small tumors and lymph node metastases[1]. A meticulous search for extra-testicular primaries is mandatory to exclude metastatic disease[13].

Histologically, TNET's exhibit solid nested, insular or trabecular growth patterns however acinar and glandular growth patterns with luminal mucin and mixed patterns may also be seen[14]. The neoplastic cells are often monomorphic with

abundant granular eosinophilic to pale cytoplasm, uniform round nuclei with fine or salt and pepper chromatin and the stroma is usually fibrous. The presence of more atypical large cells, necrosis, >2 mitoses in 10hpf and a Ki-67 proliferation index of >3% usually correlates with a diagnosis of NEC however these findings are in correlation with NEC's of other sites as there is currently no standardized categorization of TNECs[15,16]. These high-grade features may be associated with lymphovascular and perineural invasion. A complete absence of GCNIS, coupled with negative germ cell markers, supports a primary (non-GCT-related) origin. Mixed Teratoma-neuroendocrine tumors are identified by recognizing the presence of concurrent morphologically distinct germ-cell neoplasms.

Immunohistochemically, TNENs express cytokeratin (AE1/AE3, CAM5.2), neuroendocrine markers (Synaptophysin, Chromogranin A, CD56 and INSM1)[1]. INSM1 demonstrates superior sensitivity and specificity compared to conventional neuroendocrine markers[13]. Germ cell markers (OCT3/4, SALL4, PLAP and CD30) are typically negative, distinguishing NENs from GCTs [9]. The molecular profile of most TNENs remains under researched and controversial with some authors stating detection of isochrome 12p, underpinning relation with other germ-cell neoplasms, while others state the absence of the this isochrome[7,17]. Additionally the detection of this isochrome varied in pre-pubertal and post-pubertal germ-cell neoplasms.

Radical inguinal orchidectomy is both diagnostic and therapeutic for localized disease[18]. Surgery alone may be curative for organ confined disease with negative margins, but adjuvant therapy with cisplatin based regimen or radiation is recommended in the presence of vascular invasion, distant spread or high Ki-67 index[1]. Radiation therapy may also play a palliative role. Protocols and guidelines on the use of targeted and immune checkpoint therapies remain unreported for TNEN's but hold promise given molecular parallels with pulmonary NECs [4]. Reported survival data available is mostly in relation to NETs which have good prognosis with 5 year survival of more than75%[1,8]. The prognosis of NEC's is not explicitly indicated in the literature however the presence of carcinoid syndrome, distant metastases, lymph node involvement and high Ki-67 are associated with poor outcomes which can be improved on aggressive management[19].

CASE REPORT

We present the case of a 28 year old male with a left testicular mass. The patient had normal clinical levels Gonadotropin, Alpha feto-protein and LDH. The imaging, macroscopic and microscopic findings are as submitted in subsequent figures. The patient had a testicular mass with the dimensions provided in Figure 1. The histology revealed a solid tumor in nests separated by fibrous stroma. The tumor showed foci of necrosis, perineural and lymphovascular invasion. Synaptophysin and Chromogranin-A immunohistochemistry were strongly positive, confirming neuroendocrine differentiation. Negative markers included CK20, Alpha-inhibin, WT1 and Calretinin.

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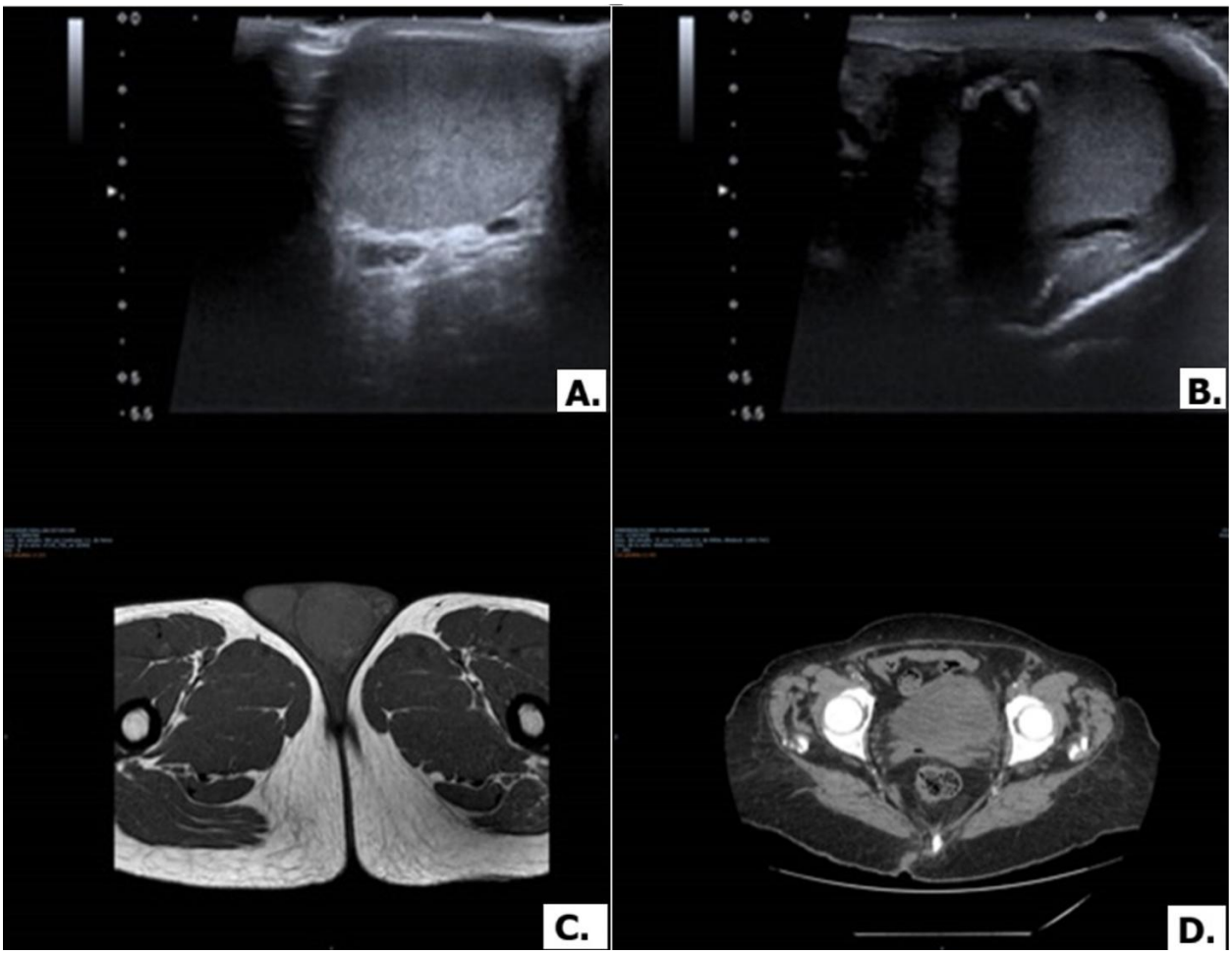

FIGURE 1. Imaging Findings

- Testicular ultrasound scan showing a mass in the left testis (A&B).
- Pelvic MRI with IV contrast was performed (C&D).
  - The left testis was enlarged with a solid nodular mass inside, occupying more than 80% of it, measuring 40 mm (RL) x 33.1 mm (AP) x 37.2 mm (CC), with low signal on T1 and T2 and enhancement with contrast, ruling out testicular tumor of the seminoma type. The right testicle was normal. There were no hydroceles or signs of epididymitis. Varicose dilation of both pampiniform plexuses was observed, with larger left venous lakes (> 5 mm), which increased with the Valsalva maneuver. The prostate, urinary bladder and scrotal wall were normal.

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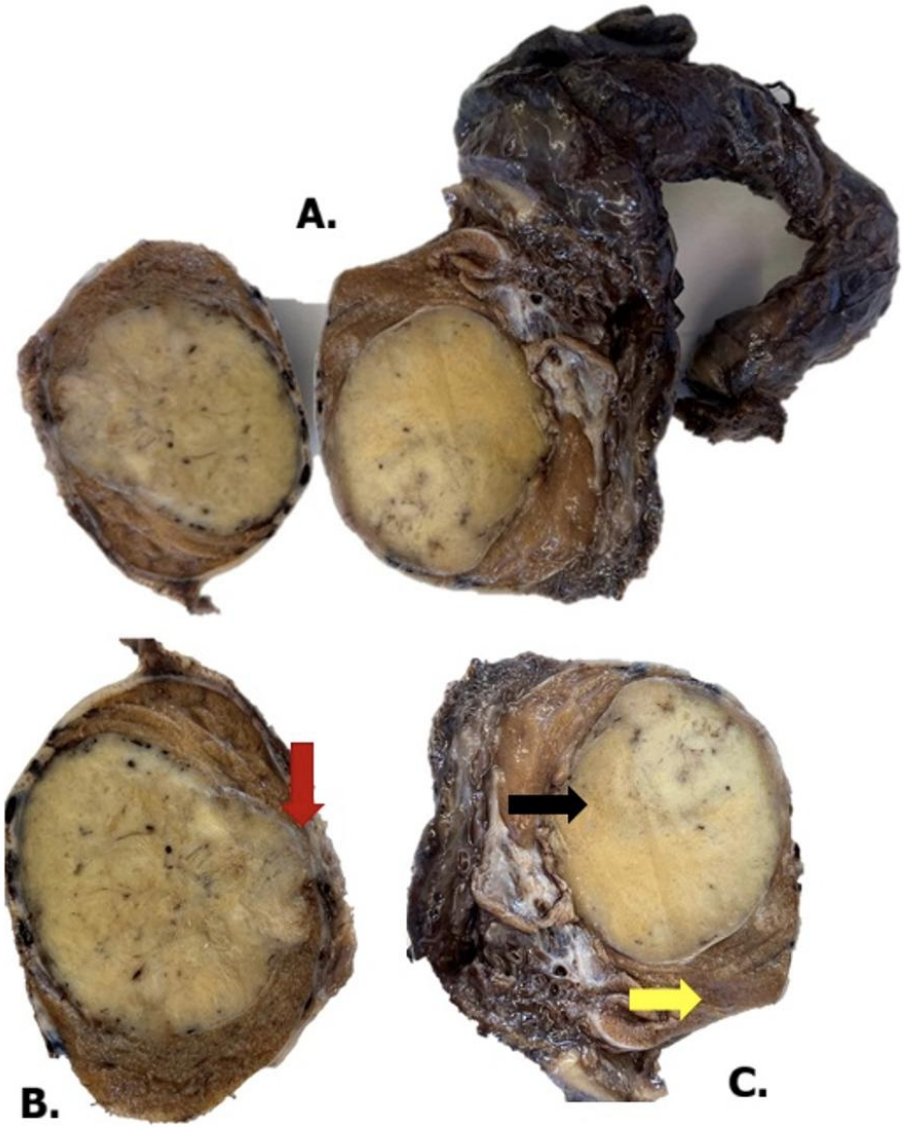

Figure 2. MACROSCOPIC FINDINGS.
Cut surface of the unencapsulated testicular tumor revealing a yellow solid nodule; Tumor size 5.1 × 4.3 cm. Testicular size 7.9 × 6.6 cm. (A). Inked spermatic code on right half of the specimen. Invasion of the tunica albuginea – red arrow (B). Unencapsulated neoplasm – black arrow, and residual normal testis – yellow arrow (C).

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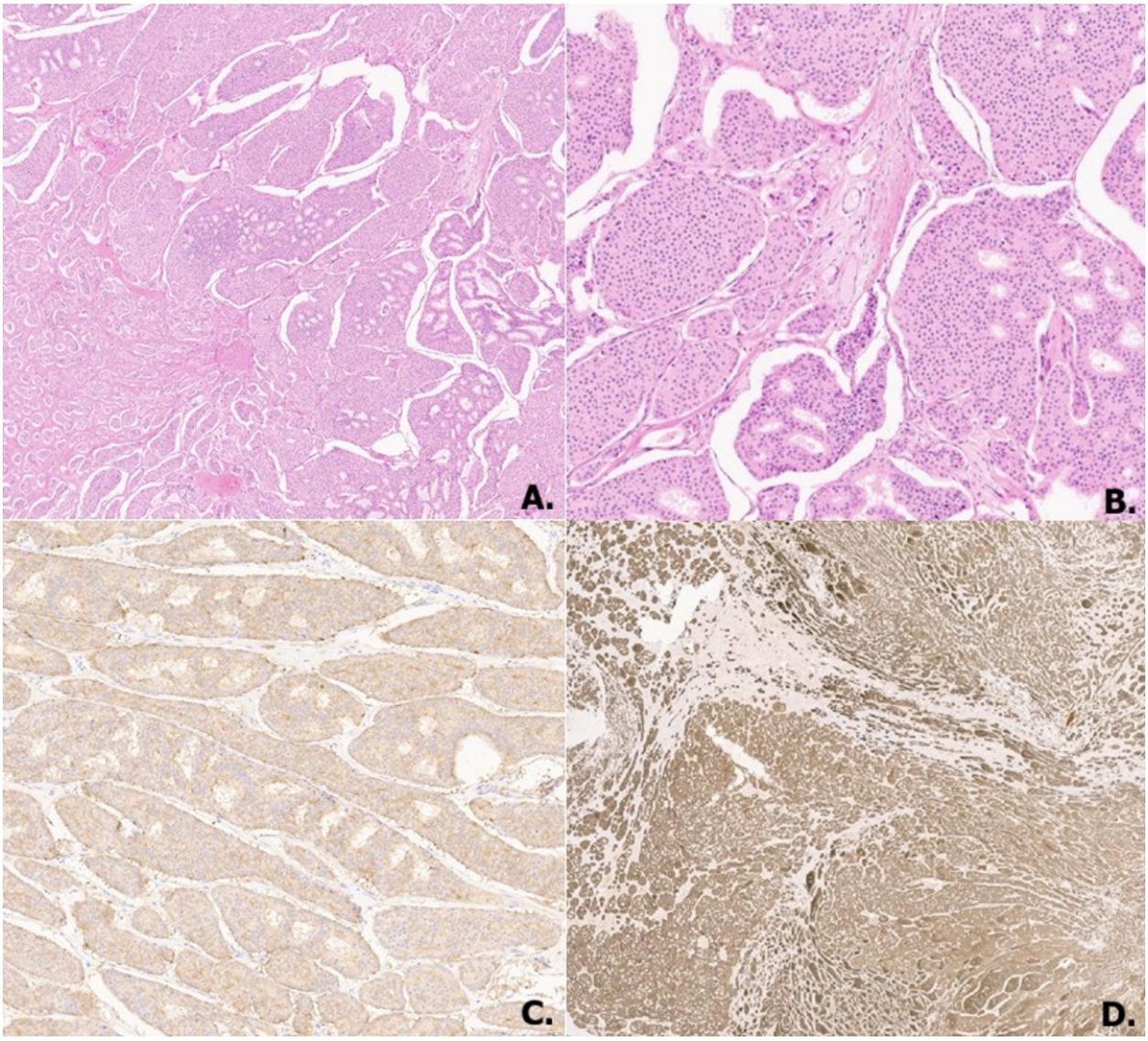

Figure 3 MICROSCOPIC FINDINGS
H&E showing well defined solid nests of monomorphic cells with abundant eosinophilic cytoplasm and round nuclei with stippled chromatin (A&B). The tumor nests are separated by fibrous stroma. The tumor showed foci of necrosis, perineural and lymphovascular invasion. Synaptophysin (C) and Chromogranin-A (D) immunohistochemistry were strongly positive, confirming neuroendocrine differentiation.

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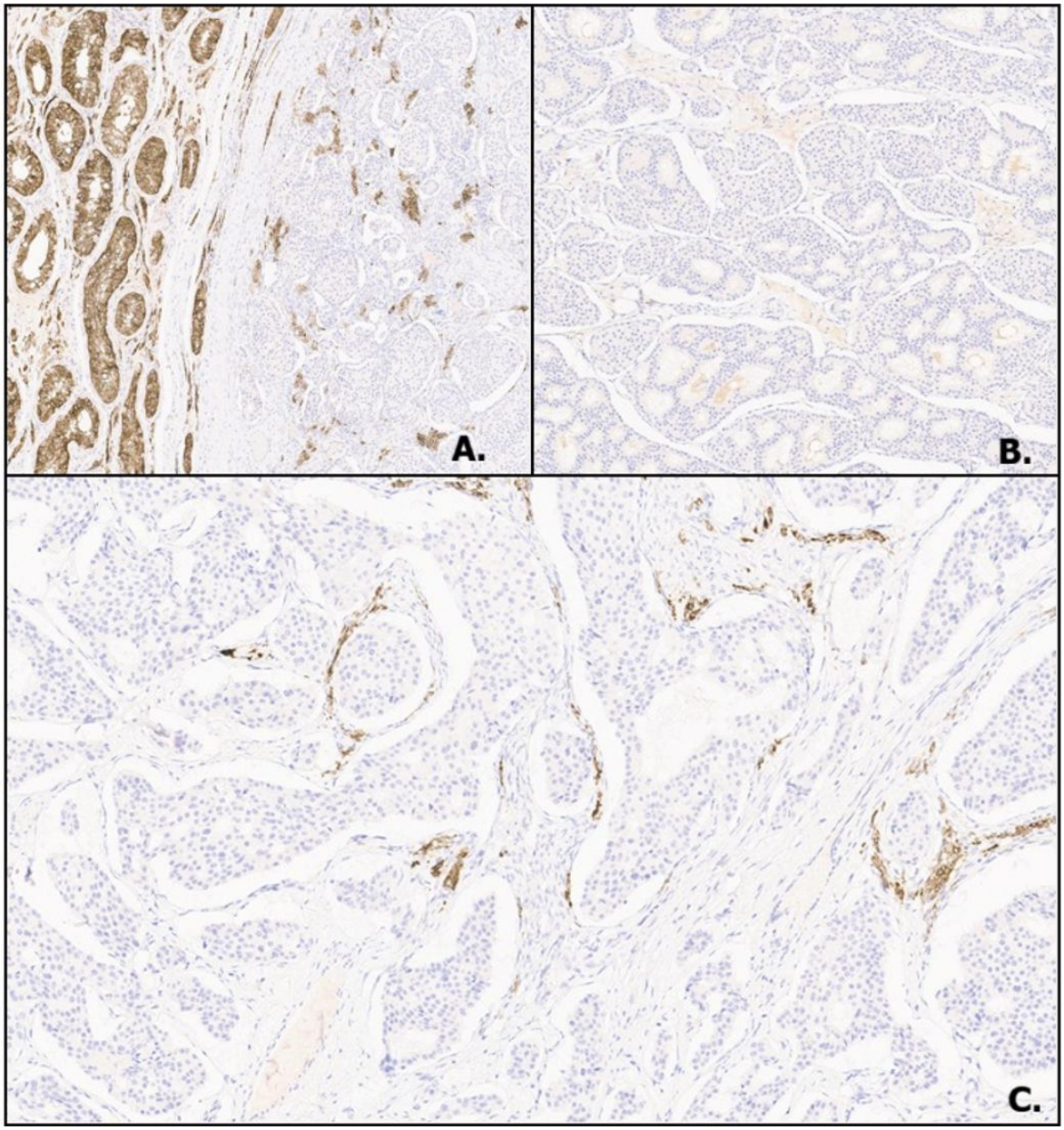

Figure 4. NEGATIVE IMMUNOHISTOCHEMISTRY MARKERS.
A) Alpha inhibin, B) WT1, C) Calretinin.

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DISCUSSION

While primary TNENs are rare, testicular NECs are even more scarce and diagnostically challenging because of mimicry of other small round blue cell tumors and the difficulty in distinguishing primary from metastatic disease[5].

Most TNET's are unilateral with equal involvement of both the right and left testis and only a few examples of bilateral NETs have been reported. First-line treatment is generally a radical orchiectomy, and on gross inspection, the tumors usually present as solid, well circumscribed, yellow homogenous scrotal masses which are unencapsulated with rare areas of calcifications and necrosis.
The imaging characteristics of TNENS remain to be specifically defined and categorized for prepubertal NET distinct from postpubertal NEC. The average reported size for TNET in one metanalysis was 3.8cm while tumors stated as "NET's" with metastases were significantly larger - 5cm and above. Ultrasonography usually reveals a well-defined solid hypoechoic testicular mass with punctate calcification in TNEN's.[1]
The main differential diagnosis is with metastatic neuroendocrine neoplasms or other organs often supported by the findings of bilateral testicular involvement with lymphovascular invasion and multiple organ spread. Other differentials include primitive neuroectodermal tumors, lymphomas and other germ-cell neoplasms[2]. A broad immunohistochemical panel incorporating epithelial, neuroendocrine, germ cell, and lymphoma markers is therefore essential with adequate sampling of the testicular tumor.

Prognostically, proliferation index and stage are the main determinants of outcome. Unlike prepubertal NETs, which are often indolent, NECs behave aggressively regardless of size[1]Poor prognostic factors include a larger tumor size, atypical tumors with increased mitotic figures, and the presence of carcinoid syndrome. Follow-up should include periodic cross sectional imaging given the risk of early relapse. Long term survivors remain rare, underscoring the need for collaborative registry data and molecular profiling[2]**.** Future work should clarify genomic landscapes, assess therapeutic biomarkers (PD-L1, DLL3), and explore novel agents such as PRRT or combination chemo-immunotherapy[20].

CONCLUSION & FUTURE DIRECTIONS

Primary neuroendocrine carcinoma of the testis represents an extraordinary diagnostic and therapeutic challenge. Accurate classification requires integration of clinical details, imaging findings, histomorphology, immunohistochemistry, and molecular features, contextualized within the WHO 2022 framework. Expanded genomic studies, multi-institutional collaboration, and standardized reporting will be vital for determining diagnostic criteria and guiding evidence based management. Pathologists play a central role in distinguishing true primary NECs from metastases and GCT derived lesions, ensuring appropriate staging and guiding therapy. Incorporation of molecular pathology and advanced imaging holds promise for future precision oncology in this rare but instructive malignancy.

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