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DICIEMBRE

PRIMARY TESTICULAR NEUROENDOCRINE CARCINOMA, NONFUNCTIONAL JUXTAGLOMERULAR CELL TUMOR, AND LYMPHOEPITHELIAL CYST OF THE THYROID: RARE ENTITIES, REFINED BY HISTOPATHOLOGY

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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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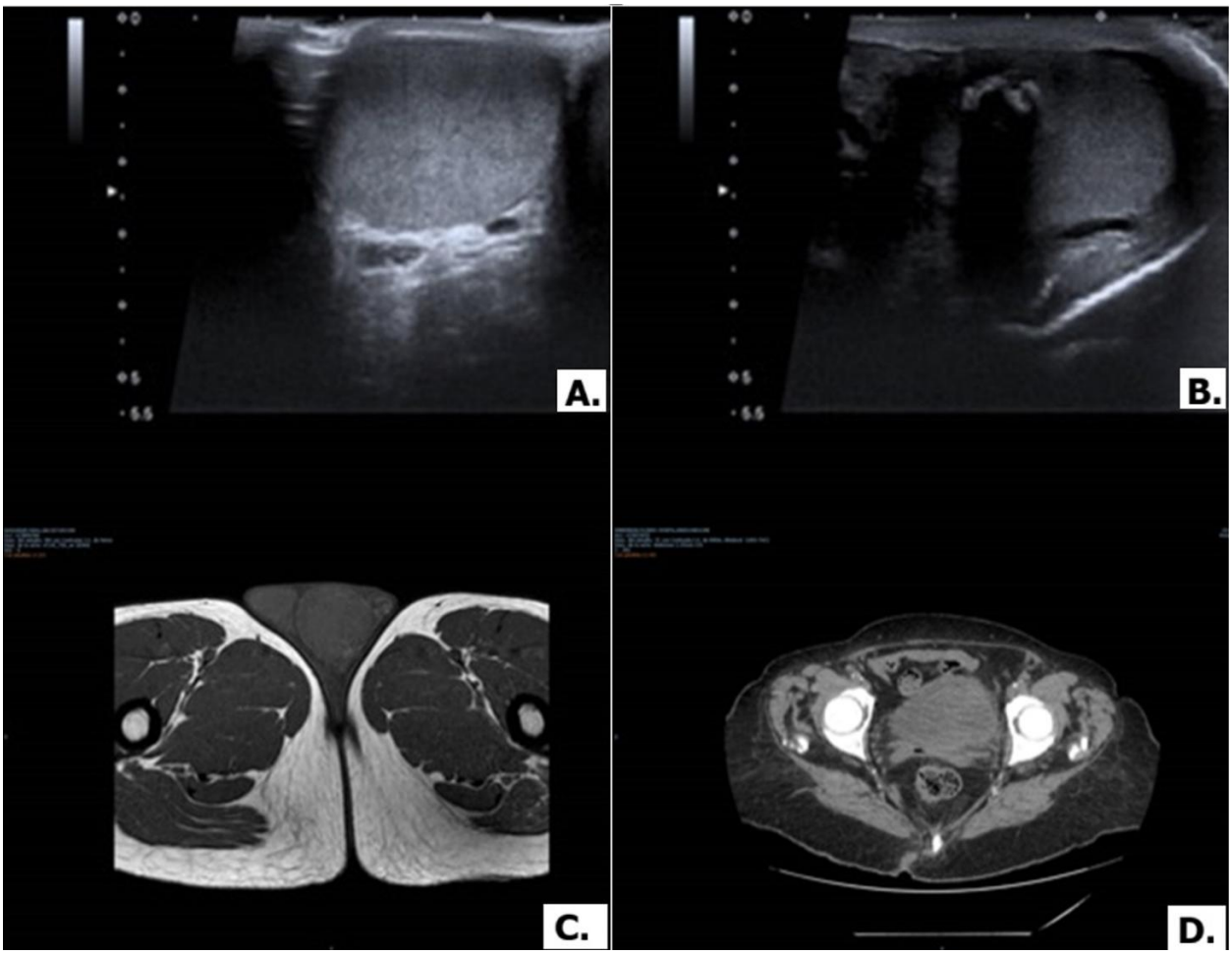

FIGURE 1. Imaging Findings

- 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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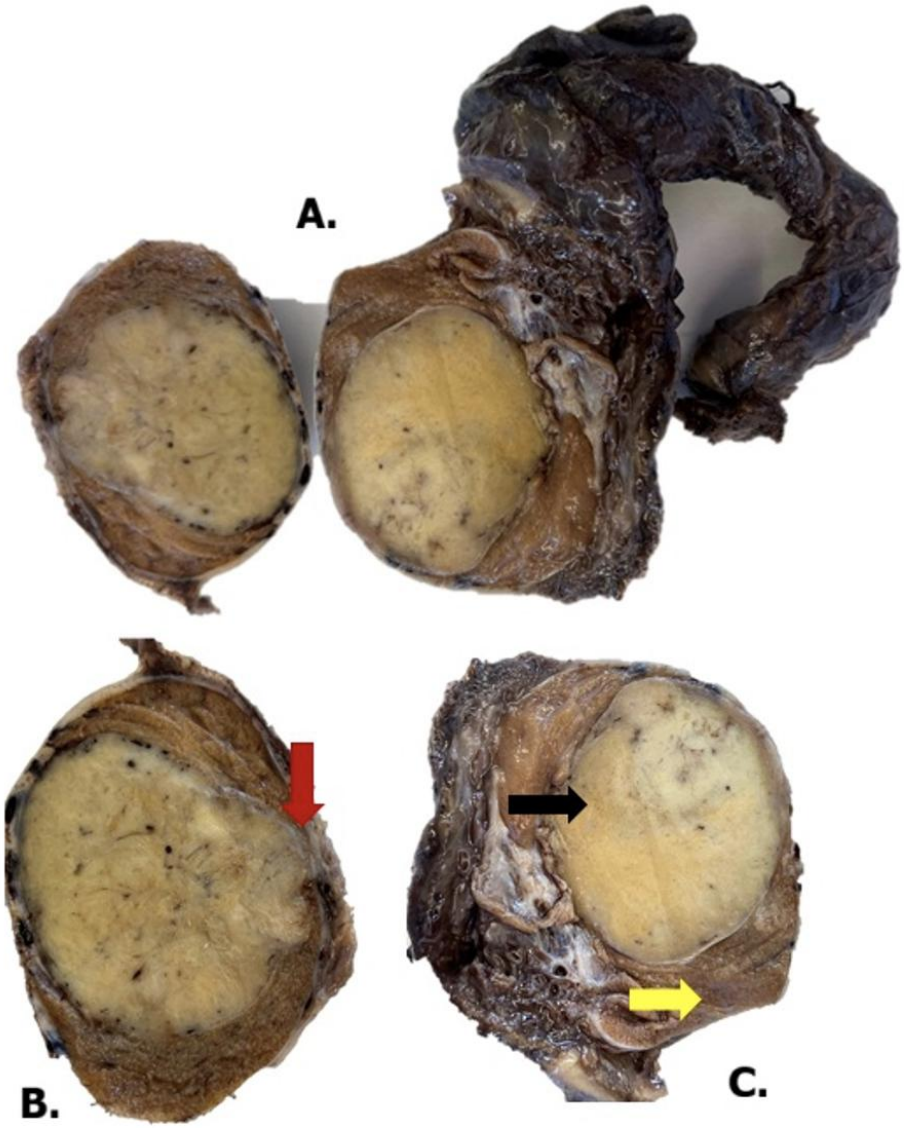

Figure 2. MACROSCOPIC FINDINGS.
Cut surface of the unencapsulated testicular tumor revealing a yellow solid nodule; Tumor size 5.1 × 4.3 cm. Testicular size 7.9 × 6.6 cm. (A). Inked spermatic code on right half of the specimen. Invasion of the tunica albuginea – red arrow (B). Unencapsulated neoplasm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

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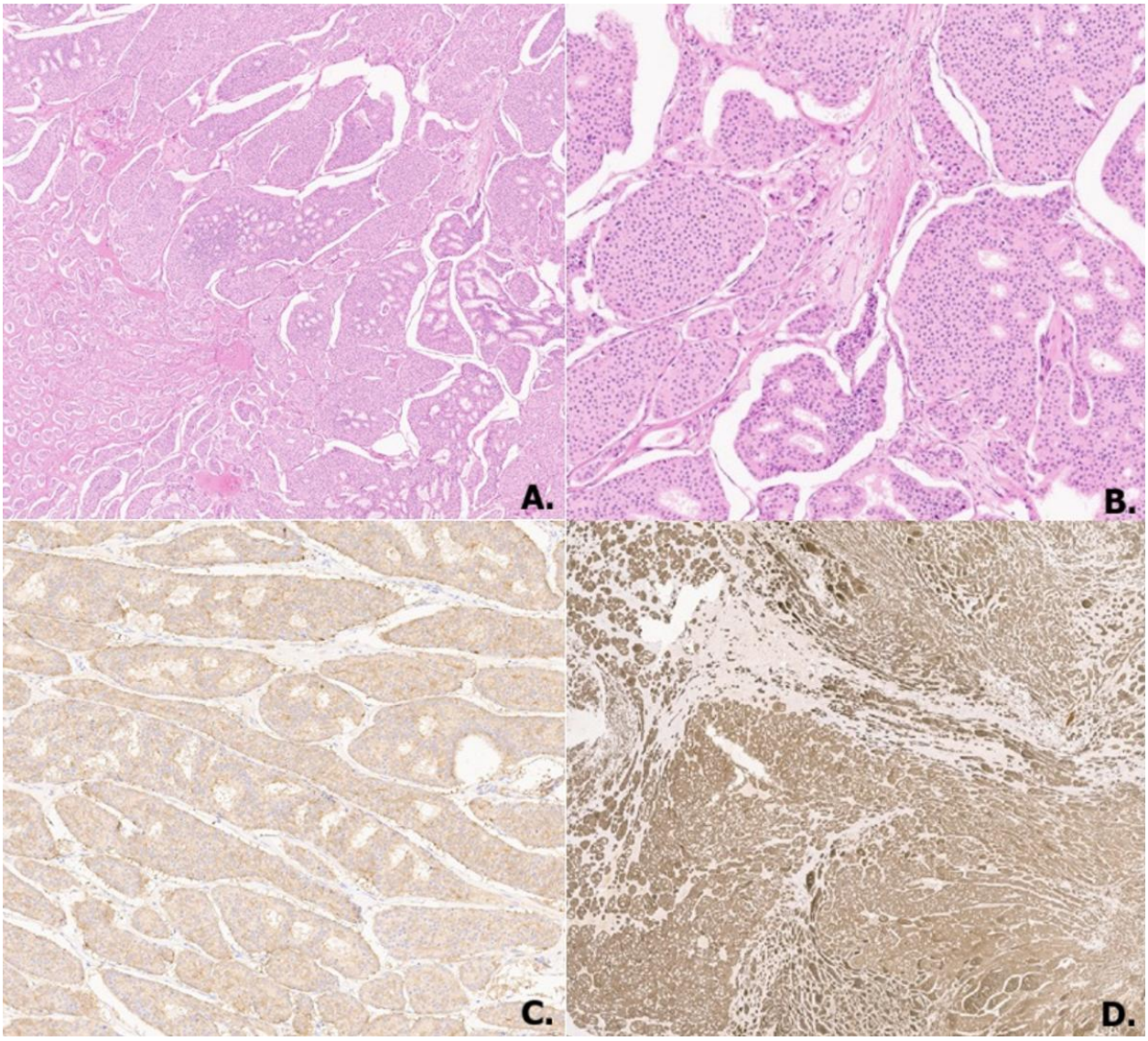

Figure 3 MICROSCOPIC FINDINGS
H&E showing well defined solid nests of monomorphic cells with abundant eosinophilic cytoplasm and round nuclei with stippled chromatin (A&B). The tumor nests are separated by fibrous stroma. The tumor showed foci of necrosis, perineural and lymphovascular invasion. Synaptophysin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

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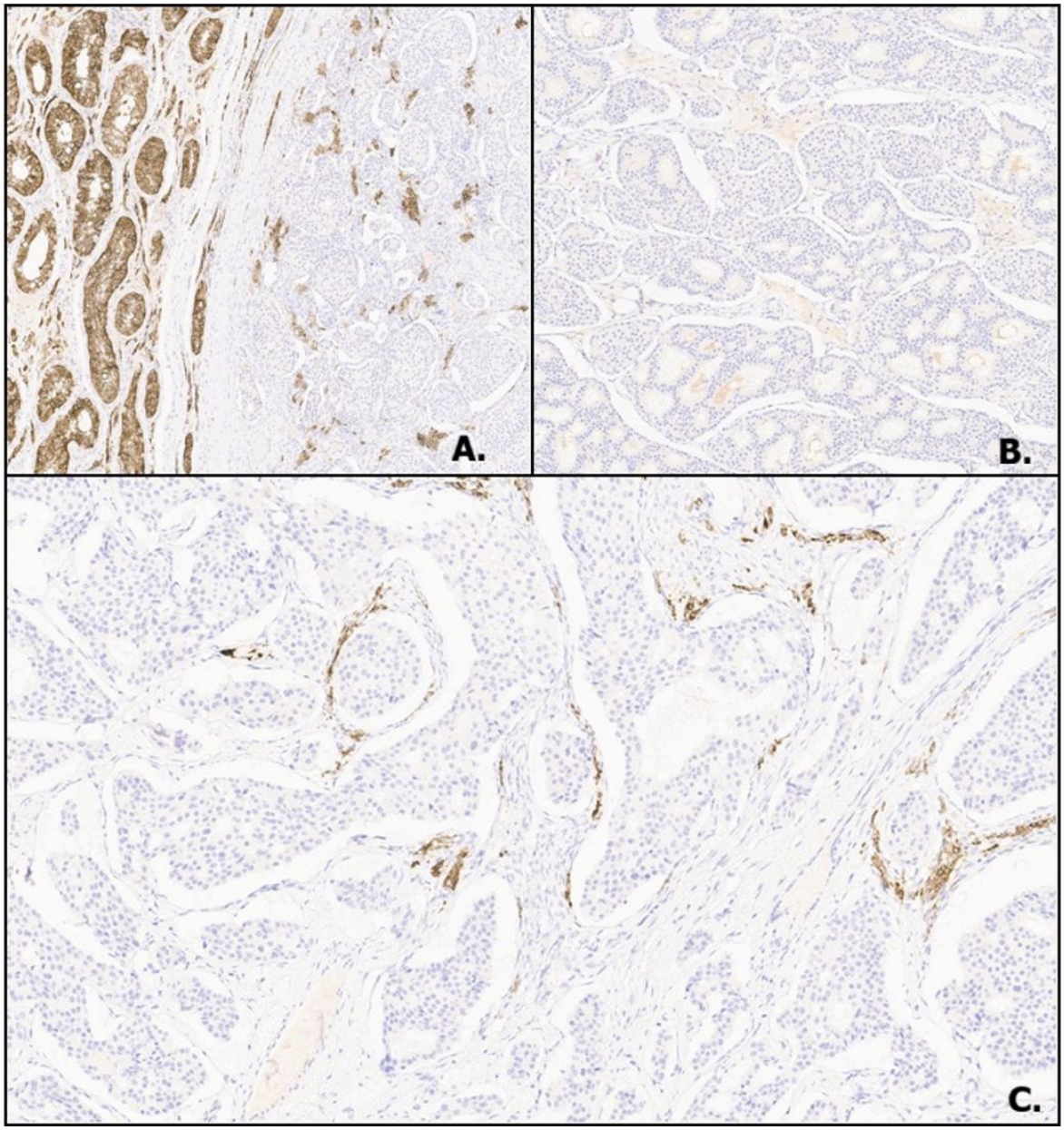

Figure 4. NEGATIVE IMMUNOHISTOCHEMISTRY MARKERS.
A) Alpha inhibin, B) WT1, C) Calretinin.

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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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TUMOR DE CÉLULAS YUXTAGLOMERULARES NO FUNCIONAL: UN IMITADOR DE CARCINOMA DE CÉLULAS RENALES. A PROPÓSITO DE DOS CASOS.

NON-FUNCTIONAL JUXTAGLOMERULAR CELL TUMOR: A RENAL CELL CARCINOMA MIMIC. REPORT OF TWO CASES.

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RESUMEN

El tumor de células yuxtaglomerulares (reninoma) es una neoplasia renal benigna poco frecuente, caracterizada por la secreción autónoma de renina, que produce hipertensión refractaria e hipocalemia frecuente. Se han reportado menos de 200 casos. Presentamos dos pacientes evaluados en un centro terciario en Medellín, Colombia, ambos inicialmente sospechados de carcinoma de células renales según las imágenes. El diagnóstico definitivo requirió histopatología e inmunohistoquímica. La resección quirúrgica produjo mejoría clínica en ambos casos. Estos casos resaltan la importancia de considerar el reninoma en pacientes jóvenes con hipertensión severa y masas renales que imitan malignidad.

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ABSTRACT

Juxtaglomerular cell tumor (reninoma) is a rare benign renal neoplasm characterized by autonomous renin secretion, leading to refractory hypertension and frequent hypokalemia. Fewer than 200 cases have been reported. We present two patients evaluated in a tertiary center in Medellín, Colombia, both initially suspected of having renal cell carcinoma based on imaging. Definitive diagnosis required histopathology and immunohistochemistry. Surgical excision resulted in clinical improvement in both cases. These cases highlight the importance of considering reninoma in young patients with severe hypertension and renal masses that mimic malignancy.

Keywords: Juxtaglomerular cell tumor, reninoma, hypersecretion of the renin hormone, renal mass, hypertension

Palabras clave: Tumor de células yuxtaglomerulares, reninoma, hipersecreción de la hormona renina, masa renal, hipertensión.

INTRODUCCIÓN

El tumor de células yuxtaglomerulares (también conocido como reninoma) es una neoplasia de comportamiento benigno que se origina en las células del músculo liso modificado de la arteriola aferente del aparato yuxtaglomerular, descrita por primera vez por Robertson et al. en 1967. Se caracteriza por la secreción continua de renina, que mantiene activado el eje renina–angiotensina–aldosterona y produce un cuadro clínico dominado por signos de hiperaldosteronismo. Entre ellos destacan la hipopotasemia, presente en aproximadamente el 80% de los casos, y la hipertensión arterial (HTA) refractaria.

Se trata de una patología poco frecuente, con cerca de 200 casos reportados en la literatura. Suele diagnosticarse entre la tercera y cuarta décadas de la vida y afecta con mayor frecuencia a mujeres, con una relación hombre:mujer cercana a 1:2 (1,2).

A continuación, presentamos la revisión y el análisis de dos pacientes con diagnóstico confirmado de reninoma en una institución de alta complejidad en la ciudad de Medellín, Colombia. Nuestros casos ilustran los diversos desafíos diagnósticos que pueden surgir en la evolución de esta rara entidad.

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CASO CLÍNICO 1

Mujer de 54 años, con antecedente de menopausia en tratamiento con tibolona, remitida al servicio de hepatología por el hallazgo incidental de un supuesto quiste pancreático en una ecografía abdominal, el cual no se asociaba a síntomas específicos. Con el fin de caracterizar mejor este hallazgo, se realizó una resonancia magnética abdominal, en la que se identificó una lesión incidental (ver Figura 1). Con estos resultados, la paciente fue remitida al servicio de urología y posteriormente programada para nefrectomía parcial derecha por laparoscopia, procedimiento que se llevó a cabo sin complicaciones.

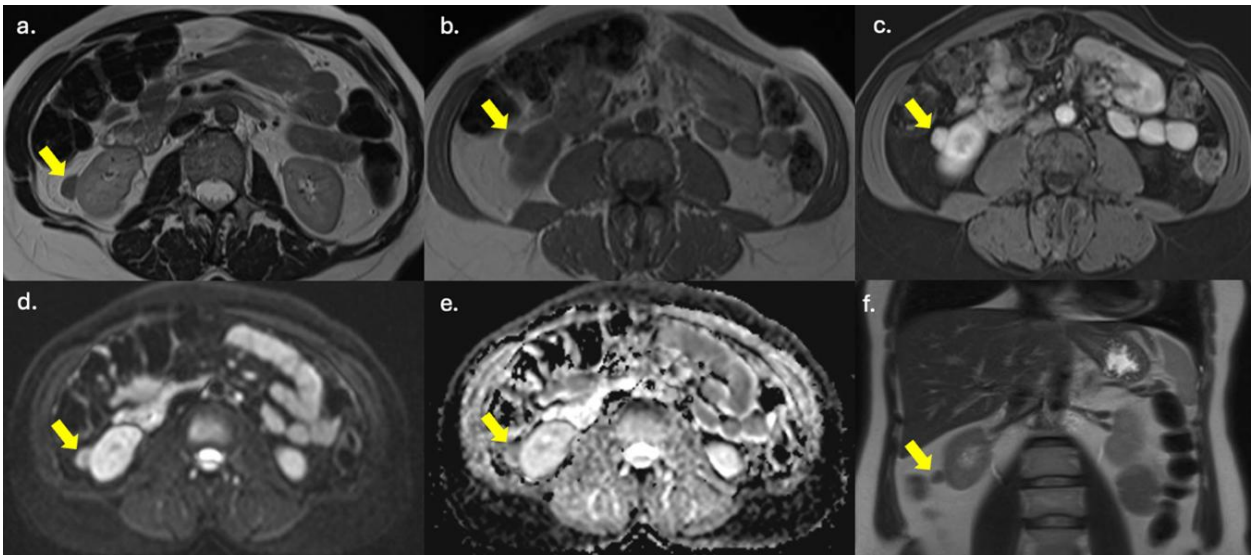

Figura 1. Resonancia magnética de abdomen. Se identifica una lesión sólida con componente quístico en el polo inferior del riñón derecho, con un diámetro máximo de 13 mm.

a) Lesión hipointensa en secuencia potenciada en T2.
b) Lesión isointensa en secuencia T1.
c) Realce tras la administración de medio de contraste.
d) Restricción a la difusión.
e) Valores bajos en el mapa de coeficiente aparente de difusión (ADC).
f) Lesión exofítica mayor del 50%, ubicada por debajo de la línea polar inferior, sin claro predominio anterior o posterior en el eje axial, y sin contacto con el hilio renal ni el sistema colector, lo que corresponde a un RENAL score de 4x.

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En el departamento de patología, se recibió la pieza de nefrectomía parcial donde se evidenció una alteración de la arquitectura renal por una lesión nodular bien delimitada, con cápsula delgada. Los cortes histológicos mostraron una proliferación celular constituida por células de citoplasma redondo, con áreas fusocelulares y estroma vascular. Las células tumorales mostraron inmunorreactividad para CD34, por lo cual se estableció el diagnóstico de tumor de células yuxtaglomerulares (reninoma). (ver Figura 2).

Otras ayudas diagnósticas útiles en el estudio de reninoma incluyen la medición de reninaplasmática no realizada en este caso debido a la baja sospecha inicial y la inmunohistoquímica para renina, la cual no se encontraba disponible en la institución.

CASO CLÍNICO 2

Paciente masculino de 57 años, remitido al servicio de urología para manejo quirúrgico tras el hallazgo incidental de una masa en el polo superior del riñón derecho en una ecografía abdominal realizada por síntomas inespecíficos. Una tomografía computarizada confirmó la presencia de un tumor exofítico de 3 cm en dicha región. El paciente no tenía antecedentes familiares de enfermedad renal ni de hipertensión de origen endocrino. Entre sus antecedentes médicos destacaban hipertensión arterial diagnosticada a los 50 años, en tratamiento con amlodipino 10 mg/día, y prostatectomía radical realizada en noviembre de 2022 por adenocarcinoma de próstata (Gleason 7, grado 3). Durante la evaluación inicial presentaba presión arterial controlada (130/72 mmHg) y un índice de masa corporal de 21.8 kg/m². La resonancia magnética mostró una masa sólida, bien delimitada, isointensa en T1 e hiperintensa en T2, con captación homogénea de contraste y restricción en el mapa de difusión. La lesión no comprometía el sistema colector renal ni las estructuras vasculares adyacentes.

Se realizó nefrectomía parcial laparoscópica derecha, logrando resección completa del tumor con márgenes libres de enfermedad. El análisis histopatológico evidenció un tumor nodular bien delimitado y encapsulado, compuesto por células uniformes con citoplasma eosinófilo y núcleo redondo. La inmunohistoquímica para renina se llevó a cabo, aunque con dificultades técnicas y reconocida baja especificidad. Los marcadores neuroendocrinos (CD56, cromogranina A y sinaptofisina) fueron negativos, lo que permitió excluir neoplasias neuroendocrinas. Con base en los hallazgos histológicos y el cuadro clínico, se estableció el diagnóstico de tumor de células yuxtaglomerulares (reninoma).

La evolución posoperatoria fue favorable. Durante los primeros días presentó distensión abdominal y cólico nefrítico secundario a coágulos, los cuales se resolvieron con manejo médico. La creatinina sérica mostró un aumento transitorio a 1.34 mg/dL, regresando posteriormente a valores normales (0.9 mg/dL). No se registraron complicaciones adicionales. En los controles ambulatorios, el paciente se mantuvo estable, sin recurrencia tumoral ni hipertensión secundaria, continuando únicamente con amlodipino 10 mg/día.

Este caso resalta la importancia de incluir el reninoma en el diagnóstico diferencial de las masas renales sólidas y demuestra la efectividad de la nefrectomía parcial como tratamiento definitivo.

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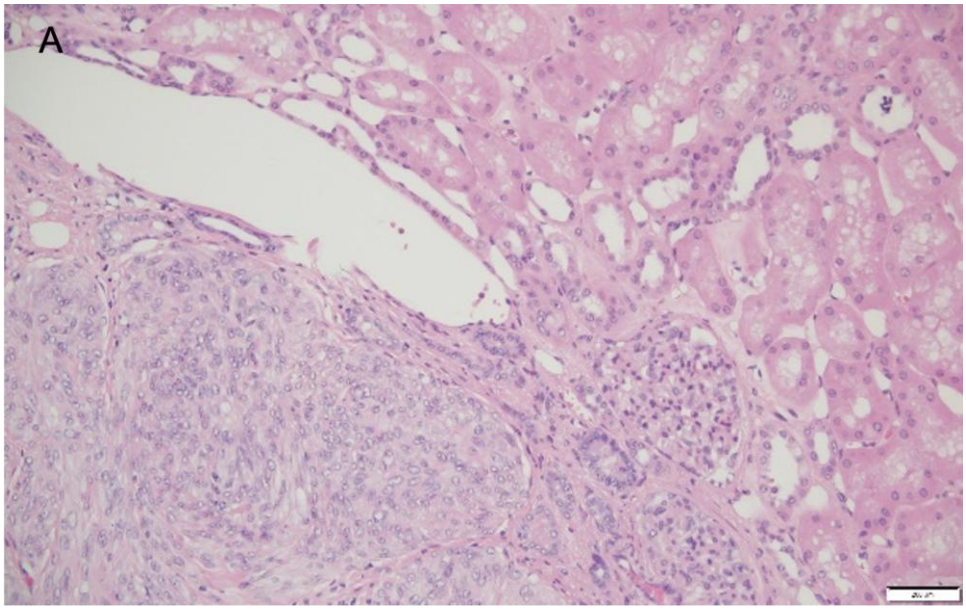
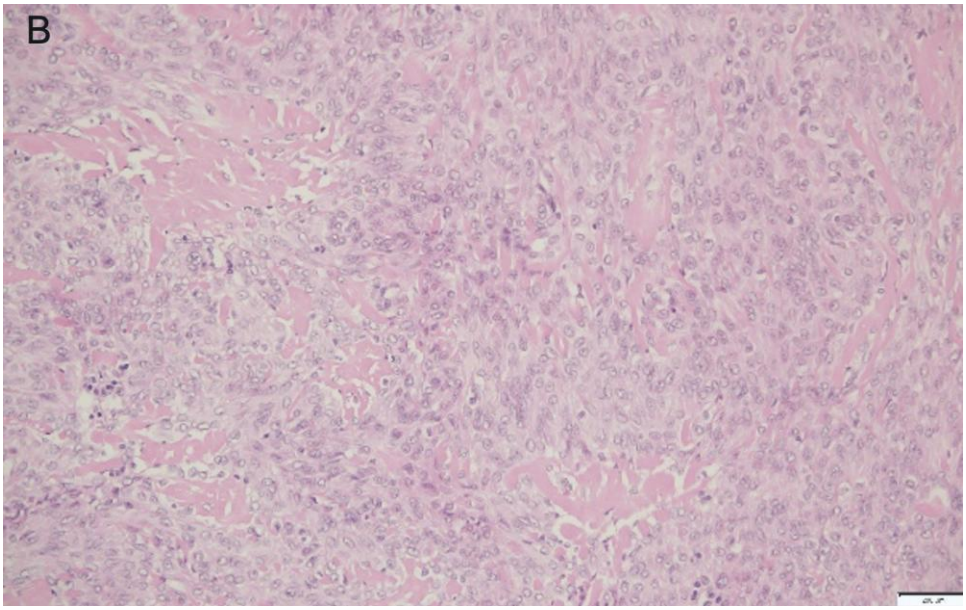
Figuras2. (A-B-C-D). Histopatología.



A. Neoplasia bien circunscrita (4x).



B. Proliferación de células con núcleos en sal y pimienta (10x).

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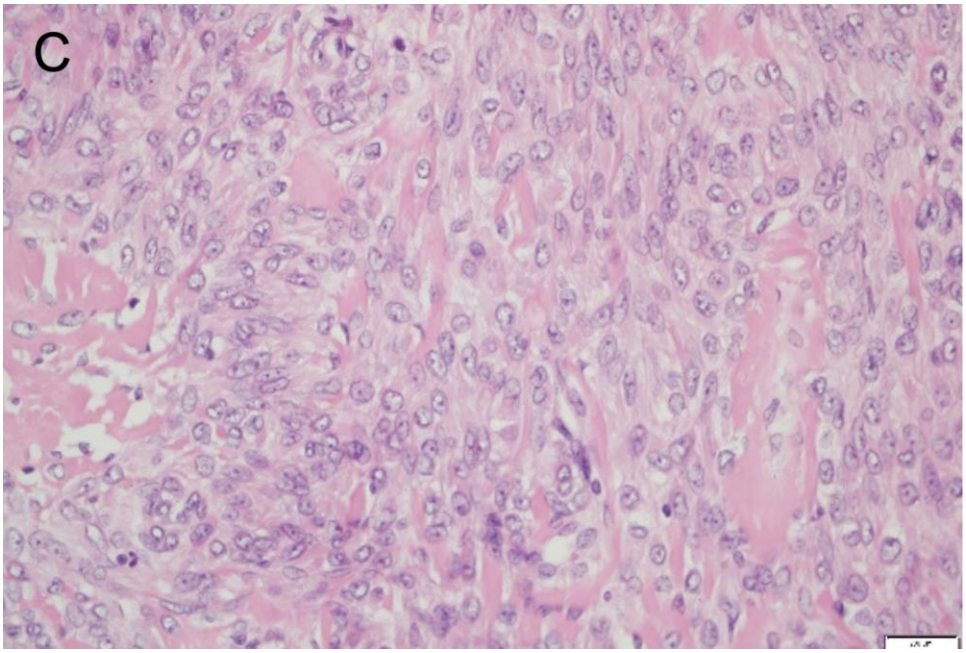
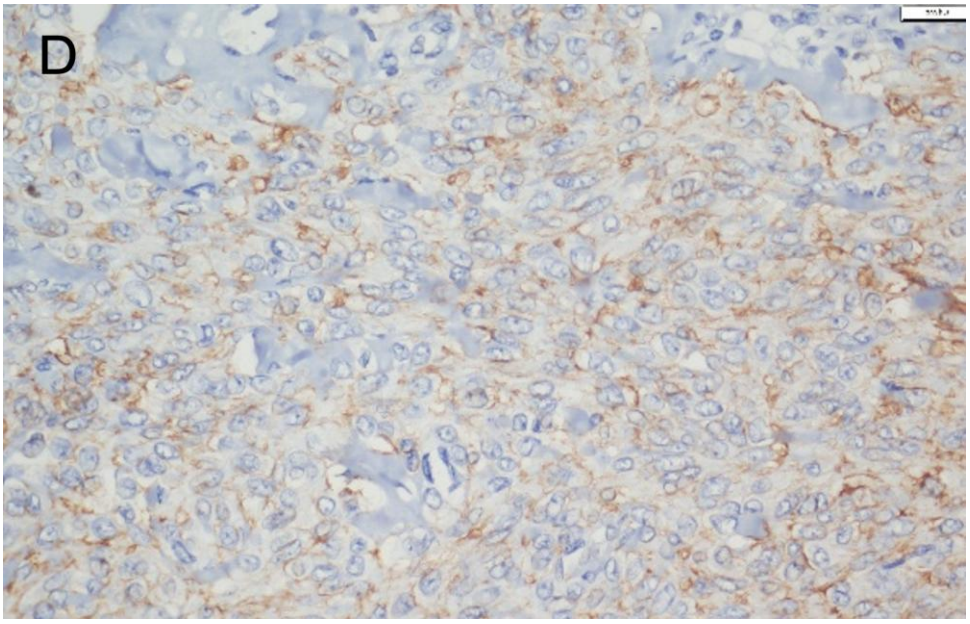


C. células poligonales, citoplasma eosinófilos, con núcleos redondos (40x)



D. Estudio de inmunohistoquímica CD56.

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DISCUSIÓN

El tumor yuxtaglomerular, o reninoma, es una neoplasia generalmente benigna que se origina en la arteriola aferente del aparato yuxtaglomerular. Se trata de una entidad poco frecuente, descrita por primera vez en 1967 (3–4), cuya prevalencia real podría estar subestimada debido al uso de fármacos que inhiben el sistema renina-angiotensina-aldosterona, ya que estos pueden enmascarar los efectos del hiperaldosteronismo (1). Afecta principalmente a mujeres, con una proporción aproximada de 2:1, y suele diagnosticarse alrededor de la tercera década de la vida, con una edad media de 27 años (2,5).

En la mayoría de los casos, la hipersecreción de renina por el tumor altera el eje renina-angiotensina-aldosterona, lo que explica su cuadro clínico característico. El aumento en la retención de sodio y agua a nivel tubular, junto con la mayor excreción de potasio, da lugar a la tríada clásica: cefalea, hipertensión arterial secundaria y refractaria, e hipopotasemia, que puede acompañarse de alcalosis metabólica (6). Además, los pacientes pueden presentar poliuria, así como síndrome de apnea obstructiva del sueño (2,4,7).

Se describen tres variantes clínicas:

1. Variante típica, la más frecuente, caracterizada por hipertensión, hiperaldosteronismo e hipopotasemia debido a los niveles elevados de renina.
2. Variante atípica, que cursa con hipertensión, pero niveles séricos de potasio normales.
3. Variante no funcional, la más rara (10% de los casos), en la que el tumor no produce alteraciones hormonales ni desencadena hipertensión o hipopotasemia (8).

Presentamos dos casos diagnosticados y manejados en una institución de alta complejidad en Medellín, Colombia, que ilustran los desafíos diagnósticos y terapéuticos asociados a los tumores de células yuxtaglomerulares, especialmente cuando se trata de variantes no funcionantes que pueden enmascarar el diagnóstico.

El Caso 1 corresponde a una mujer de 54 años, posmenopáusica, con una lesión renal incidental inicialmente interpretada como un posible quiste pancreático. Estudios posteriores identificaron una masa de 13 mm en el polo inferior del riñón derecho. La lesión fue resecada mediante nefrectomía parcial laparoscópica, y el análisis histopatológico confirmó un tumor de células yuxtaglomerulares.

El Caso 2 describe a un hombre de 57 años con una masa exofítica de 3 cm en el polo superior del riñón derecho, detectada durante la evaluación por síntomas inespecíficos. Tras realizar una nefrectomía parcial laparoscópica, el análisis histopatológico también confirmó un reninoma.

Aunque ambos tumores se encontraban localizados dentro del riñón, las presentaciones

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clínicas y las rutas diagnósticas variaron, destacando la heterogeneidad en la detección de estas neoplasias poco frecuentes. La hipertensión arterial estuvo presente en ambos pacientes; sin embargo, ninguno presentó hipopotasemia, un hallazgo clásico comúnmente asociado con reninomas.

Las modalidades de imagen, particularmente la resonancia magnética, fueron fundamentales para localizar y caracterizar las lesiones, las cuales se observaron como masas hiperintensas en secuencias T2 e iso- o hipointensas en T1. Aunque no se midieron niveles séricos de renina por limitaciones logísticas, el diagnóstico se sustentó en los hallazgos histológicos característicos, incluidos la morfología tumoral típica y la positividad para CD34. Ambos pacientes mostraron una evolución postoperatoria favorable sin recurrencia tumoral.

Estos casos subrayan la importancia de un enfoque multidisciplinario para el diagnóstico y manejo de estas neoplasias raras. Ambos pacientes evolucionaron favorablemente tras el tratamiento quirúrgico, y los resultados refuerzan el papel de la nefrectomía parcial como una opción terapéutica definitiva y preservadora de órgano en tumores de células yuxtaglomerulares.

El abordaje del paciente inicia con estudios de extensión para hipertensión secundaria y con la realización de imágenes orientadas a la búsqueda de la etiología; sin embargo, como en este caso, también puede presentarse en forma de incidentaloma. Dependiendo de la sospecha clínica y de los recursos disponibles, se inicia con ecografía, tomografía computarizada (TC) o resonancia magnética (RM).

El hallazgo imagenológico puede dificultarse debido al tamaño del tumor, ya que suele ser muy pequeño y las masas menores de 0,5 cm representan un reto diagnóstico (3). Además, pueden confundirse con quistes renales, porque en la TC la densidad del tumor puede ser hipodensa o isodensa respecto a la médula renal, similar a los quistes. Esto puede resolverse mediante RM (1). En la RM, los tumores de células yuxtaglomerulares se observan como lesiones sólidas, pequeñas, solitarias, bien delimitadas, hiper o isointensas respecto al parénquima renal en secuencias potenciadas en T2. Pueden contener tejido necrótico o hemorrágico, generando intensidad de señal heterogénea. Presentan valores bajos en el mapa ADC, lo cual indica restricción a la difusión, y un realce temprano sin lavado, que se mantiene en las secuencias dinámicas tardías poscontraste (9).

La localización habitual es en el parénquima renal y hacia la periferia. A pesar de su vascularización, su drenaje pericapsular, ubicación y pequeño tamaño dificultan su identificación por angiografía (10).

La mayoría de estos tumores presentan una cápsula fibrosa, identificable por su baja intensidad de señal en T2, lo que los hace casi indistinguibles de los tumores de células renales. No obstante, pueden valorarse ciertos diferenciales, como la ausencia de caída de señal en las secuencias fuera de fase por su bajo contenido adiposo, o un valor de ADC mayor

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debido a la densidad celular característica del tumor de células yuxtaglomerulares (11).

Otros estudios diagnósticos descritos en pacientes con una masa renal asociada a hipertensión secundaria incluyen el muestreo selectivo de venas renales para medición directa de renina mediante radiología intervencionista. Alternativamente, puede medirse la renina sérica en sangre periférica (1).

Una vez establecido el diagnóstico, se selecciona el tratamiento, que idealmente consiste en la resección quirúrgica del tumor. En caso de contraindicación o alto riesgo quirúrgico, puede considerarse manejo farmacológico en casos seleccionados. Se ha descrito como el método óptimo la nefrectomía parcial por vía retroperitoneal laparoscópica, dado el carácter benigno y el tamaño del tumor, que generalmente mide entre 2 y 5 cm. Según su localización, tamaño y vascularización, podría optarse por nefrectomía radical en casos específicos debido al riesgo de hemorragia (1).

Otra opción terapéutica descrita es la ablación por radiofrecuencia, que ha mostrado buenos resultados en reninomas pequeños y profundos en la corteza renal (1).

Posterior al tratamiento quirúrgico, independientemente de la técnica utilizada, los pacientes suelen presentar mejoría significativa de los síntomas, y hasta el 90% no requiere medicamentos antihipertensivos después de la cirugía. El 10% restante continúa requiriéndolos debido a hipertensión primaria o a comorbilidades como el síndrome de apnea obstructiva del sueño o el hiperaldosteronismo primario (1–3).

Finalmente, el estudio anatomopatológico confirma el diagnóstico. Se observa un citoplasma redondo, ovalado o poligonal, eosinofílico, con núcleos redondos y mínima atipia. La inmunohistoquímica permite excluir diagnósticos diferenciales como carcinoma de células renales, tumor glómico o angiomiolipoma epitelioide, mediante marcadores como SMA, STAT6, desmina, cromogranina, PAX8 y HMB45. Los reninomas suelen mostrar positividad para marcadores asociados a tumores de células B, como CD34 (1, 4–5).

Otros estudios diagnósticos que se han descrito para los pacientes con una masa renal asociada a HTA secundaria en estudio, es el uso del muestreo de venas renales o prueba de renina, el cual consiste en que mediante radiología intervencionista se toma una muestra de directamente de los vasos renales y se realiza una medición de renina sérica. Otro método usado es la medición de renina sérica, pero con una muestra de sangre periférica (1).

CONCLUSIÓN

Aunque el reninoma es una entidad poco frecuente, debe considerarse en el diagnóstico diferencial de pacientes con hipertensión arterial e hipocalemia de etiología no renovascular. La identificación precisa del tumor mediante tomografía computarizada y/o resonancia

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magnética es fundamental, dado que se trata de una lesión con excelente respuesta al manejo quirúrgico.

Cuando la cirugía no es factible, la ablación por radiofrecuencia constituye una alternativa eficaz, especialmente en tumores pequeños y de localización profunda. La intervención adecuada no solo permite la normalización de la presión arterial y de los parámetros bioquímicos, sino que también contribuye a reducir el riesgo de daño a órganos diana a largo plazo.

La sospecha clínica oportuna, el abordaje diagnóstico integral y la selección adecuada del tratamiento son esenciales para mejorar el pronóstico y la calidad de vida de estos pacientes.

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LYMPHOEPITHELIAL CYST OF THE THYROID GLAND AS AN UNCOMMON CONDITION WITH CLINICAL SIGNIFICANCE: CASE REPORT AND BRIEF REVIEW OF THYROID CYSTIC LESIONS.

QUISTE LINFOEPITELIAL DE LA GLÁNDULA TIROIDES COMO UNA CONDICIÓN POCO COMÚN CON RELEVANCIA CLÍNICA: REPORTE DE CASO Y BREVE REVISIÓN DE LAS LESIONES QUÍSTICAS TIROIDEAS.

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RESUMEN
Los quistes linfoepiteliales de la tiroides (LEC-T) son lesiones tiroideas benignas poco frecuentes que representan un reto diagnóstico debido al amplio diagnóstico diferencial de los nódulos tiroideos quísticos. Histológicamente, se asemejan a un quiste del saco branquial, con un revestimiento de epitelio escamoso estratificado y, en ocasiones, áreas de metaplasia ciliada. Se han documentado pocos casos en la literatura, con frecuencia asociados a tiroiditis linfocítica crónica (tiroiditis de Hashimoto). En este artículo presentamos el caso de un LEC-T de gran tamaño en un paciente sin características de tiroiditis.

ABSTRACT
Lymphoepithelial cysts of the thyroid (LEC-T)are rare benign thyroid lesions that are diagnostically challenging due to the broad differential diagnosis of cystic thyroid nodules. Histologically, it resembles a branchial pouch cyst with a lining of stratified squamous epithelium, occasionally exhibiting areas of ciliated metaplasia. A limited number of cases have been documented in the literature, frequently in relation to chronic lymphocytic thyroiditis (Hashimoto's thyroiditis). In this article, we report a case of a large LEC-T in a patient without features of thyroiditis.

Keywords: Thyroid cyst, thyroid nodule, lymphoepithelial cyst, solid-cystic thyroid lesion, thyroid pathology.
Palabras clave: Quiste tiroideo, nódulo tiroideo, quiste linfoepitelial, lesión tiroidea sólido-quística, patología tiroidea.

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INTRODUCTION

The availability of advanced diagnostic imaging techniques has resulted in a rise in the diagnosis of thyroid nodules, the majority of which are identified incidentally and in healthy individuals[1].Thyroid nodules are benign in more than 90% of affected individuals,asymptomatic and more common among women with a female to male ratio of 4:1[2].By imaging, most thyroid nodules can be categorized as solid or solid-cystic nodules which usually carry a higher risk of malignancy or entirely cystic lesions which are usually benign[3].

A cyst is defined as a cavity lined by epithelium with fluid or semisolid material occupying the cyst cavity. Embryogenic defects, infections, tissue degeneration and neoplastic mechanisms are implicated in the formation of many cysts. Thyroid cysts are fluid-filled cavitary lesions that may vary in size, and can occasionally exhibit rapid growth [4]. Heterogeneous lesions comprising both solid and fluid components necessitate thorough evaluation by individuals skilled in imaging and cytopathology techniquesin order to determine potential indications for a fine-needle aspiration biopsy (FNAB), ideally in accordance with EU-TIRADS criteria. This is particularly important as lesions with a minimum of 50% solid component have shown a higher risk of malignancy compared to entirely solid lesions of equivalent size [5]. Malignancies arising in thyroid nodulesusually originate from the solid component of a solid-cystic nodule or concurrently with other solid thyroid nodules [6].

The main management of assymptomatic thyroid cysts measuring <3-4 cm includes observation and close clinical follow-up with imaging to monitor for any changes. Additionally, aspiration with sclerotherapy (ethanol instillation or other ablative techniques) yields better outcome as an effective method of management of simple thyroid cysts when compared with simple aspiration due tofrequent reaccumulation[7,8]. Thyroid surgery effectively excises thyroid cysts however it is usually reserved for specific clinically determined situationssuch as numerous large cysts that are visually conspicuous or symptomatic for the patient [9].

The differential diagnosis of a cystic lesion in the thyroid encompasses nodular thyroid disease (colloid goiter) with cystic degeneration, benign and malignant thyroid neoplasms exhibiting cystic changes (adenomas, carcinomas), intrathyroid parathyroid cysts, intrathyroid thyroglossal duct cysts, intrathyroid thymic cysts, epidermal inclusion cysts, parasitic cysts (particularly Echinococcus), thyroid metastasis, and lymphoepithelial thyroid cyst (LEC-T) as discussed in this article.

LEC-T is a benign cystic lesion of the thyroid, with a lining primarily composed of stratified squamous epithelium, which may be keratinizing or nonkeratinizing. Less frequently, respiratory epithelium forms the lining of these cysts. The cyst wall shows characteristic lymphoid aggregates, frequently with germinal centers [10]. The occurrence of LEC-T is rare. Since their initial description in 1989 [11], only a few dozen cases have been documented in the global medical literature. The rarity of LEC-T sometimes leads to delayed and missed diagnoses, therefore each new, well-documented case provides essential information, enhancing our understanding of its pathophysiology, clinical presentation, and appropriate care. In this article authors introduce a case report of patient with this rare condition.

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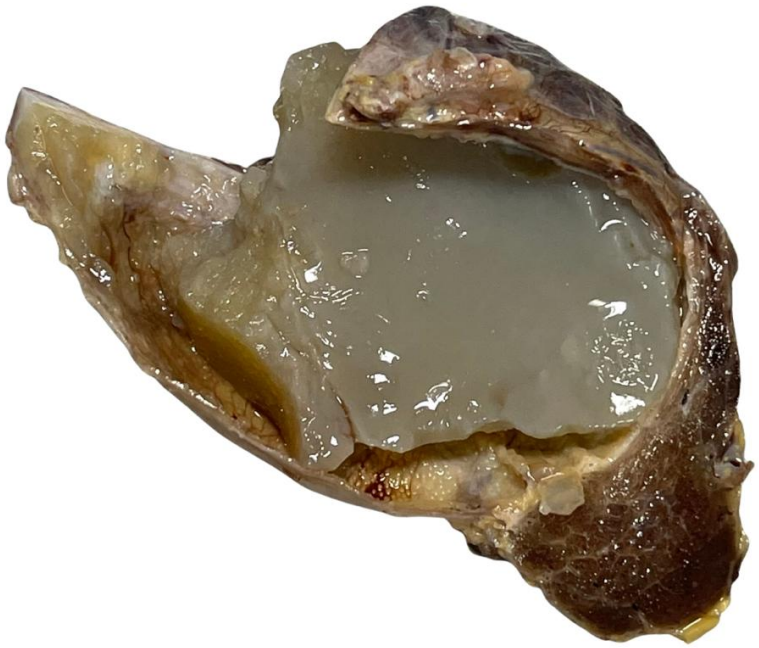
CASE REPORT

A 43-year-old man, a moderate smoker for 23 years, consulted his primary care physician after discovering a painless lump in his neck, without any accompanying symptoms. He stated that the lesion had enlarged over the past two months. An ultrasound of the neck identified a cystic lesion in the right thyroid lobe, measuring 4 cm at its largest dimension, with no accompanying calcifications (EU-TIRADS 2). The remaining thyroid gland exhibited no notable abnormalities, and lymphadenopathy was not detected. Following normal laboratory test results, the patient was scheduled for surgery – the patients underwent a right partial lobectomy with satisfactory postoperative recovery.

The submitted portion of the right lobe of the thyroid measured 5.0 × 3.0 × 2.0 cm and exhibited a deep brown, nodular capsular surface. Sectioning revealed unilocular cystic cavity measuring up to 4.5 cm in maximum diameter with a smooth inner lining. The cyst contained clear gelatinous fluid. Calcification was not observed in the walls of the cyst, and the residual tissue was firm and red-brown. Figure 1. illustrates the macroscopic appearance of the cyst.

Figure 1: Macroscopic findings of the thyroid lymphoepithelial cyst as received at the laboratory.



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Histological sections were prepared and stained with hematoxylin and eosin.

Microscopic examination revealed a benign stratified squamous epithelial lining overlying an extensive band of lymphoid cells in the cyst wall, with focal lymphoid aggregates containing well-defined germinal centers present **(Figure 2.)**.

The cyst cavity showed amorphous eosinophilic debris with some neutrophils and macrophages, **(Figure 2.a. to 3a.).**

Occasional anucleate squames are also seen in the lining epithelium and cyst debris. Entrapped atrophied thyroid follicles are seen on the exterior aspect of the cystic wall**(Figure 2c.)**.

Normal thyroid parenchyma is also seen proximal to the cyst **(Figure 2c.)**. p63 and p40, immunohistochemistry performed, showed strong positive staining in the lining epithelium confirming squamous cell origin **(Figure 3. b. & c.) -** a clear, positive nuclear reaction is seen in the cells of the stratified squamous epithelium that lines the cyst. TTF-1 nuclear staining was positive within both the lining epithelium and the entrapped thyroid follicles, adding supportive evidence of the origin of the cyst **(Figure 3. d.)**.

The cytological and immunohistochemical findings are specific and confirmatory for LEC-T, which was the definitive diagnosis provided.

Except for hormone replacement therapy with levothyroxine, the patient did not require any further treatment following the diagnosis.

A follow-up thyroid ultrasound revealed no new lesions in the remnant of the right lobe and the entire left lobe of the thyroid.

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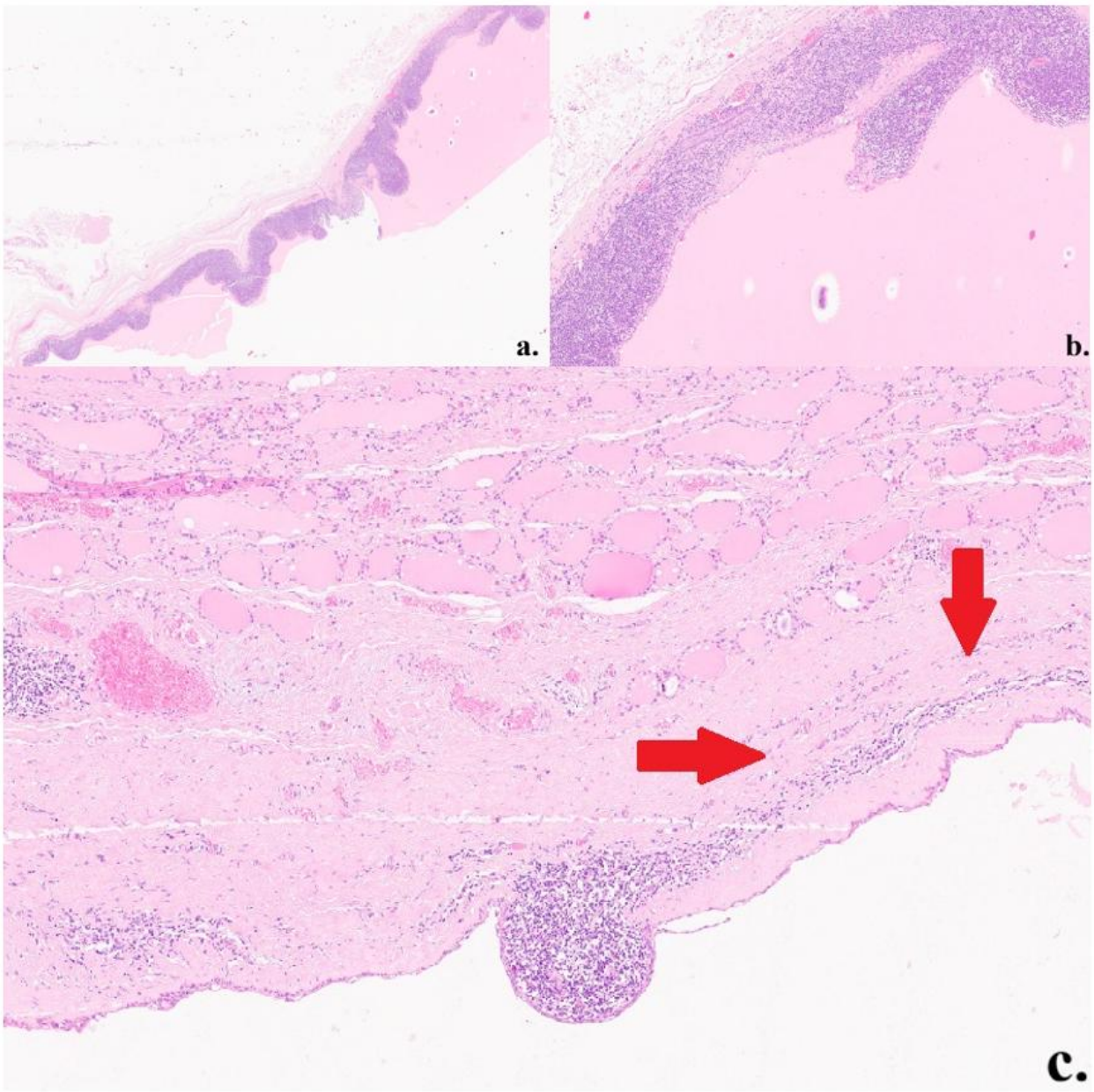

Figure 2. Low power view photomicrographs of benign stratified squamous epithelial lining and extensive lymphoid tissue within the fibrous cyst wall (images **a.** and **b.**). Image **c.** with entrapped thyroid follicles within the cyst wall (red arrows).

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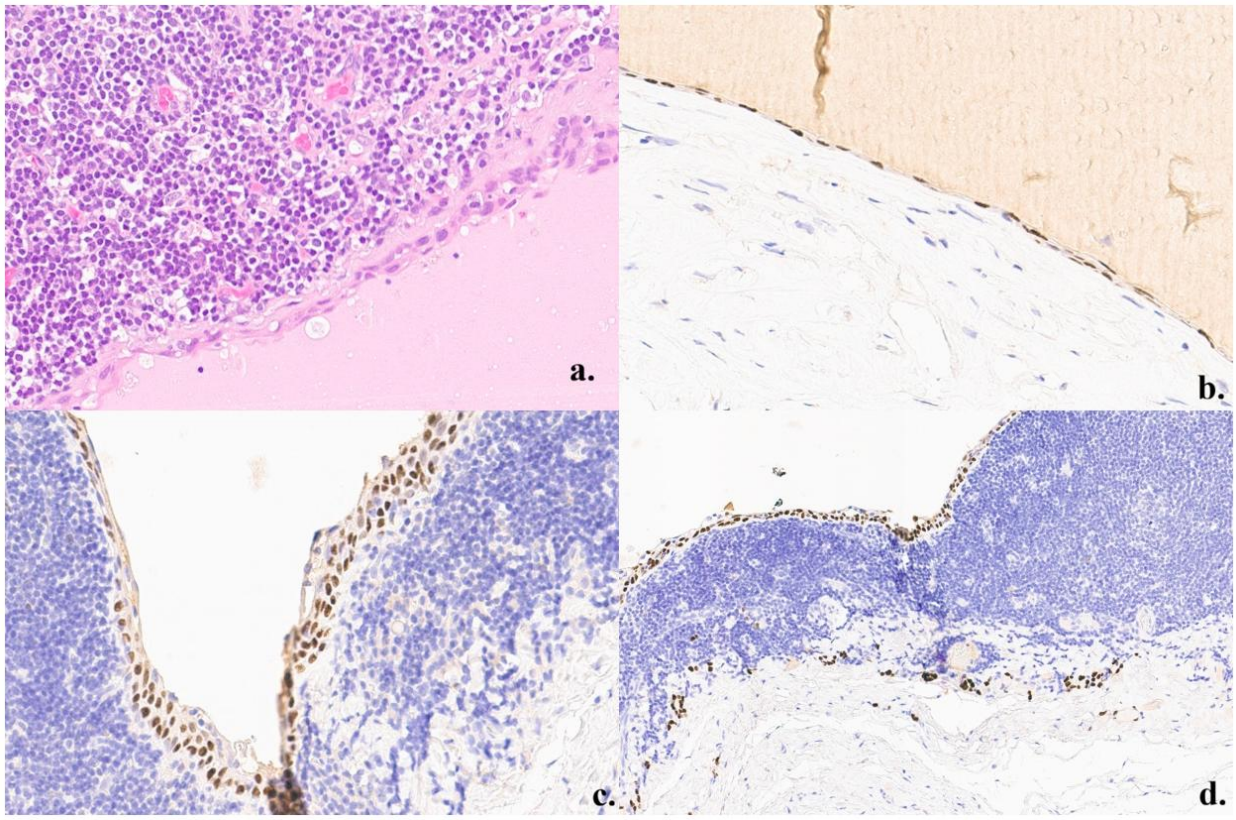

Figure 3. Higher power views of the cyst with proteinaceous content in the cyst cavity **(image a.)**. Immunohistochemistry; images **b.**p40, **c.**p63, **d.**TTF-1 highlighting entrapped follicles.

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Discussion.

An accurate preoperative diagnosis of LEC-T is often challenging owing to the fact that these cysts are rare and present with overlapping clinical and imaging features with other benign and neoplastic thyroid cysts/cystic nodules. This underscores the clinical significance of this benign entity. LEC-T usually manifests clinically as a vague, gradually enlarging, and asymptomatic thyroid nodule that cannot be differentiated by palpation from more prevalent diseases [10]. Imaging studies, particularly ultrasonography, which are crucial instruments in assessing thyroid nodules, may yield false positive findings for malignancy. On imaging, LEC-T presents as an anechoic cystic lesion, however it may occasionally manifest as a pseudo-solid lesion or a nodule with many hyperechoic foci exhibiting acoustic shadowing, which might be misinterpreted as calcifications and heighten the suspicion of malignancy [12,13]. Likewise FNAB, the gold-standard early screening modality which provides critical information regarding risk of malignancy, frequently yields Bethesda I (unsatisfactory) or III (atypia of undertermined significance) categories, further complicating clinical decision making. The presence of squamous cells and lymphocytes is not limited to this cyst and therefore careful macroscopic and microscopic evaluation of aspirates to exclude other diagnoses with similar cytology is paramount. The differential diagnosis on cytology includes and intrathyroidal thyroglossal duct cyst, branchial cleft cyst, cystic thymic remnant,primary or metastatic malignancies including squamous, anaplastic and uncommon subtypes of papillary thyroid carcinoma [11,14–16].

The etiopathogenesis of LET-C has been a focal point of intense scholarly discourse for years, resulting in the emergence of two conflicting ideas. Historically, the prevailing idea stated that LEC-T arises from ectopic remnants of the branchial apparatus, which were entrapped in the thyroid gland parenchyma during its descent in development. The justification for this theory was the histological resemblance of LEC-T to lateral neck cysts which arise within remnants of the third, fourth or fifth branchial pouch, from which solid cell nests develop in the thyroid gland. The existence of additional branchial-derived structures within the thyroid parenchyma, including ectopic thymus or parathyroid tissue, further strengthened this hypothesis [10,11,17,18]. However, more recent studies using advanced immunohistochemical techniques have cast serious doubt on this theory - revealing that the solid cell nests and epithelial cells of typical lateral neck cysts display a distinct immunohistochemical profile in contrast to LEC-T. The primary distinction is the absence of expression of immunomarkers in the epithelial cells of the branchial structures of other cysts which are typically expressed in thyroid tissue, including thyroglobulin, TTF-1 and PAX-8[16,19]. Variations in the topography of these lesions have been noted, with solid cell nests predominantly situated in the upper and central regions of the thyroid lobes, while LEC-T are more frequently found in the middle and lower regions. The strong clinical and histological connection between LEC-T and Hashimoto's thyroiditis offers more evidence. Research indicates that as much as 95.2% of LEC-T cases are accompanied with characteristics of chronic lymphocytic thyroiditis, with more than 85% of patients exhibiting serologically verified Hashimoto's thyroiditis [19]. It is crucial to acknowledge that this association clarifies the paradox presented by the branchiogenic theory. The metaplastic changes suggest that a cyst is not

an independent embryonic structure activated by inflammation, but is a direct consequence of this inflammatory process, which affects native thyroid cells [20]. Consequently, LEC-T should be regarded not as an embryogenic anomaly, but as an uncommon, acquired reactive lesion primarily resulting from severe autoimmune thyroiditis. In our patient's case however, features of autoimmune thyroiditis were absent in the portion of the right lobe submitted for histopathology evaluation.

While LEC-T typically presents as a standard simple cyst (characterized by an anechoic, well-defined lesion with a thin wall and posterior acoustic enhancement), it may also manifest as a hyperechoic, pseudo-solid lesion on ultrasound due to the dense, proteinaceous contents comprising exfoliated keratin, cellular debris, and cholesterol crystals. In exceptional instances, tightly packed keratin aggregates may reflect ultrasonic waves with such intensity that they obstruct further transmission, resulting in an acoustic shadow behind the lesion, characteristic of true calcification despite its absence. In both scenarios, the lesion will be classified as EU-TIRADS-3 rather than the standard EU-TIRADS-2 designation (or even an EU-TIRADS-5 designation), prompting clinicians to pursue more invasive diagnostics and heightening the patient's stress levels [5,12,13,21]. The dense and viscous nature of the cystic contents typically renders FNAB non-diagnostic (Bethesda category I) due to the poor diagnostic yield of cellular material for analysis [22,23]. Wherean adequate aspirate is available, cytological characteristics overlap with other disease entities which may also present with mature benign squamous epithelial cells, frequently anucleate (referred to as keratinous scales), abundant lymphocytic infiltrate, and a dense, granular, or amorphous background, consistent with aggregates of keratin [24]. The occurrence of squamous cells typically serves as a significant diagnostic clue, as this type of epithelium is not ordinarily found in the thyroid gland. Diagnosis involves meticulous algorithms and criteria which focus on distinguishing LEC-T from: primary differentiated carcinomas of the thyroid with squamous differentiation, metastases of squamous cell carcinoma to the thyroid, anaplastic carcinoma with squamous differentiation, mucoepidermoid carcinoma, Warthin-like subtype of papillary thyroid carcinoma, and other lesions aforementioned in the introduction of this article [16,25]. A working knowledge of the wide differential diagnosis of LEC-T on FNABavoids unnecessarily ascribingneoplastic Bethesda categories V or VI which invariably result in the recommendation for unwarranted aggressive surgical interventions[23].

Typically, cystic lesions of the thyroid gland are predominantly colloid nodules, which are benign proliferations of normal glandular tissue with brown cyst content macroscopically. The cystic transformation inside these nodules is a secondary occurrence arising from hemorrhagic events, necrosis, and liquefaction within the enlarged follicles. In contrast, the cyst content of LEC-T appears mucinous on gross examination of histology specimen. The pathognomonic ultrasound sign of a colloid nodule, strongly indicating its benign nature, is the presence of numerous, small, echogenic foci corresponding to thickened colloid, which generate a characteristic "comet tail" artifact [26,27]. Although colloid nodules are more prevalent, it is important to note that both adenomas and malignant thyroid cancers can also undergo cystic transformation implying that this particular macroscopic characteristic does not rule out malignancy [28,29]. A critical aspect of the

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diagnosis is ultrasound risk stratification, which aims to determine eligibility for FNAB by evaluating the morphology of any solid component, its margins, echogenicity, presence of microcalcifications, shape, and other characteristics [5,27,29]. About 5% of cystic nodules identified as thyroid cysts do not arise from the follicular epithelium but from the parathyroid glands; these cysts may be indicated by the color of the cystic fluid, which is typically, but not invariably, as transparent as water. The definitive diagnosis is established by identifying elevated levels of parathyroid hormone and low or undetectable levels of thyroglobulin in the aspirated fluid [30]. Another cyst with a potential extrathyroidal origin is the thyroglossal duct cyst, typically situated in the midline of the neck, remnants may infrequently become entrapped within the thyroid parenchyma. The ultrasonography characteristics are nonspecific and do not facilitate a dependable distinction from other thyroid cystic lesions. The cytological analysis of the aspirate may reveal benign squamous cells and inflammatory cells, indicative of the epithelial lining of the persistent duct [31]. Cysts of ectopic thymic tissue within the thyroid are also frequently observed in the pediatric demographic. Ectopic thymus is an ultrasound mimic of malignancy, characterized by multiple pinpoint internal echoes that may imply microcalcifications. The true origin of these internal echoes however are ultrasound wave reflections from adipose tissue interspersed with lymphoid tissue. The cytological morphology is characteristic due to the presence of Hassall's corpuscles, pathognomonic for thymic tissue [32,33]. Extremely rare benign lesions arising from the migration of ectodermal tissue into the thyroid gland may manifest as epidermal inclusion cysts. These cysts can result from trauma, surgical procedures, or the entrapment of embryonic remnants. Because of the variability in ultrasound imaging, they may occasionally mimic malignant lesions; however, the cytological analysis following FNAB typically reveals a distinctive profile, characterized by the presence of mature, superficial squamous cells, anucleate keratinous masses, and keratin debris in the background, particularly after the collection of purulent or bloody material [34]. Parasitic thyroid cysts and hydatid disorders are exceedingly rare, with just over 50 documented occurrences, primarily linked to Echinococcus granulosus, which can access the thyroid gland via the liver and lungs. FNAB is not advised due to the potential danger of distributing cyst fluid and inducing anaphylactic shock; however, this concern is based on a singular report in the literature documenting an allergic reaction following FNAB[35]. We must also consider the potential, although infrequent, cystic metastases of cancer to the thyroid - the most prevalent cancers that metastasize to the thyroid are renal cell carcinoma, breast cancer, lung cancer, and melanoma; however, it is challenging to confirm which of these most frequently induces cystic alterations [36].

The rapid expansion of these lesions and the frequent difficulty in ruling out malignancy at an early stage render surgical intervention the predominant treatment option. The prognosis for individuals with LEC-T is excellent. The lesion is benign, with no reported cases of malignant changes. Recurrence does not occur following full excision. It is crucial to acknowledge that these patients, frequently diagnosed with Hashimoto's disease, necessitate adequate endocrine surveillance [10]. The presence of autoimmune thyroiditis elevates the likelihood of further problems, including the onset of thyroid lymphoma [37]. Although this pertains to the

broader illness setting rather than LEC-T specifically, it underscores the necessity for ongoing patient surveillance.

Conclusions

LEC-T is an uncommon, benign clinicopathological condition whose pathophysiology, as indicated by recent investigations, is most likely associated with squamous metaplasia within thyroid follicular cells within the background of thyroiditis. It presents a considerable diagnostic problem due to its clinical and radiological features closely resembling malignancy, and the outcomes of fine-needle aspiration biopsy are frequently ambiguous, raising oncological apprehensions. It is also essential for every practicing clinician to be aware of the need for differential diagnosis of cystic lesions.

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A RARE CAUSE OF SPONTANEOUS PERIRENAL HEMORRHAGE: REVISITING WUNDERLICH SYNDROME.

CAUSA RARA DE HEMORRAGIA PERIRRENAL ESPONTÁNEA: REVISIÓN DEL SÍNDROME DE WUNDERLICH.

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ABSTRACT
Wunderlich syndrome (WS),defined as spontaneousnon-traumatic renal or perirenal hemorrhage is a rare but potentially life-threatening condition first described by Carl Reinhold August Wunderlich in 1856. The common underlying causes include Primary renal neoplasms, vascular lesions, and coagulopathies. Contrast-enhanced computed tomography (CT) remains the standard imaging modality forclinical evaluation and histopathologic examination confirms the underlying etiology, informinglong-term management and prognostication. Therapeutic options include conservative management, selective arterial embolization, and surgery depending on hemodynamic stability and underlying cause with minimally invasive interventions becoming the standard of care. Integrating radiologic, surgical, and histopathologic insights is crucial for timely diagnosis and optimal outcomes.This case report adds to the body of literature on this rare clinical entity and highlights clinicopathological features, etiologic mechanisms, diagnostic approaches, and management strategies of WS in a patient with a left adrenal mass.

RESUMEN
El síndrome de Wunderlich (SW), definido como hemorragia renal o perirrenal espontánea no traumática, es una entidad poco frecuente pero potencialmente mortal descrita por primera vezpor Carl Reinhold August Wunderlich en 1856. Las causassubyacentesmáshabitualesincluyenneoplasiasrenalesprimarias, lesiones vasculares y coagulopatías. La tomografía computarizada (TC) con contraste continúa siendo la técnica de imagen de referencia para la evaluación clínica, mientras que el estudio histopatológico confirma la etiología y orienta el manejo y el pronóstico a largo plazo.

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Las opciones terapéuticas comprenden manejo conservador, embolización arterial selectiva y tratamiento quirúrgico, según la estabilidad hemodinámica y la causa de base, con técnicas mínimamente invasivas que se han convertido en el estándar de atención. La integración de los hallazgos radiológicos, quirúrgicos e histopatológicos es esencial para un diagnóstico oportuno y resultados óptimos. Este caso contribuye a la literatura sobre esta infrecuente entidad clínica y subraya las características clínico-patológicas, los mecanismos etiológicos, las estrategias diagnósticas y las opciones de tratamiento del SW en un paciente con una masa suprarrenal izquierda.

Keywords: Wunderlich syndrome (WS), Peri-renal hemorrhage, Angiomyelolipoma (AML), renalcell carcinoma (RCC), Computed Tomography (CT).

Palabras clave:Síndrome de Wunderlich (SW), hemorragiaperirrenal, angiomiolipoma (AML), carcinoma de célulasrenales (CCR), tomografíacomputarizada (TC)

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INTRODUCTION

Wunderlich syndrome (WS), also known as spontaneous renal hemorrhage, is defined as bleeding into the subcapsular or perirenal space without antecedent trauma.[1]It presents as a medical emergency with significant diagnostic and therapeutic challenges that bridge multiple specialties, including and not limited to urology, radiology, and pathology.[2] The syndrome most frequently arises secondary to solid renal masses including renal angiomyolipoma (AML) and renal cell carcinoma (RCC), but can also occur in patients with coagulopathies, vascular disease and adrenal tumors.[3,4]

Angiomyolipoma, a benign mesenchymal tumor composed of smooth muscle, fat, and dysmorphic vessels, accounts for nearly half of all WS cases.[5]Thedelicate vessels in AML lack elastic tissue, rendering them susceptible to aneurysmal dilation and rupture.[6] In contrast, RCC-related hemorrhage typically results from tumor necrosis, vascular invasion, or fragile neovascularization.[7] Other pathophysiological mechanisms involved in the emergence of WS may include cyst rupture, vasculitis and hypertensive vascular injury.[8] Idiopathic WS, though rare, may reflect microvascular fragility or unrecognized cystic pathology within the Kidneys.Rare cases have been seen in pregnancy however the underlying cause was attributed to AML.[9]

The common presentation in WS is acute flank pain, a palpable mass, and hypovolemic shock—a triad known as Lenk's triad, which classically occurs in less than 20% of cases.[10]Owing to the rarity of the disease, a diagnosis can be missed even in patient's presenting with features of the classical triad.[11] This underscores the need for a high index of suspicion of WS and standardized robust diagnostic algorithms for WS which currently do not exist.

Imaging via CT scan is a highly accurate first choice method for identifying and localizing renal and perirenal hemorrhage however an underlying etiology may not always be identified on imaging alone. CT scan imaging is also useful in guiding percutaneous drainage of the hematoma and follow-up examinations, providing details on the evolution of the hematoma. Typical CT findings in WS vary with the stage of the hematoma and include avascular isoechoic to hyperechoic fluid collections in the acute bleeding or hypoechoic to anechoic fluid collections with septations and heterogeneity in the subacute and chronic hematomas. Color Doppler ultrasound Scan is an affordable option for the identification of active bleeding while magnetic Resonance Imaging (MRI) can differentiate subacute hematomas from neoplastic lesions. CT scan may also identify a well-defined lipid rich mass in AML or an enhancing tumor mass with calcification in RCC. While CT scan is the preferred imaging modality, US scan and MRI are also useful and multimodality evaluation is often superior in comparison to single modality imaging [12,13]

Because radiological assessment does not always provide diagnostic information and clinical lesions may share overlapping imaging characteristics, Histopathologic confirmation is essential, especially where there is high suspicion for malignancy. The diagnostic material may be a large surgical resection of affected organs or identified masses but where minimally invasive clinical interventions are opted, TRU-CUT biopsies can be utilized reliably in specific situations.[14,15]

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Histopathological analysis remains indispensable for accurately identifying the cause of WS, by providing essential information about the nature of any underlying lesions and differentiating benign from malignant causes. In AML, histological sections demonstrate triphasic morphology comprising smooth muscle bundles, mature adipose tissue, and thick-walled vessels lacking elastic lamina.[16] Immunohistochemically, AML cells express HMB-45 and Melan-A, distinguishing them from RCC. RCC-associated WS exhibits malignant epithelial cells with cytoplasmic clearing or granular eosinophilia, often with necrosis and hemorrhage.[17]RCC variants may contain hemosiderin-laden macrophages and areas of cystic degeneration.

In rare instances, retroperitoneal hemorrhage arises from adrenal tumors or cysts which have ruptured and elicit secondary tissue changes.[18] However only a few of these cases have been classified as WS arising from primary adrenal lesions.[3,19]

Management of WS is not standardized and largely depends on hemodynamic stability of the patient, extent of hemorrhage, and underlying etiology. Conservative treatment is reserved for stable patients with small, self-limiting hematomas.[5,11] Selective arterial embolization has emerged as the preferred first-line intervention for ongoing hemorrhage, achieving hemostasis while preserving renal function.[20] Surgery, such as partial or radical nephrectomy, is indicated when embolization fails or where malignancy is suspected. Prognosis largely depends on the underlying cause; AML-related WS generally carries an excellent prognosis, whereas RCC-related cases have variable outcomes. A recent series reported survival rates exceeding 90% with appropriate multidisciplinary management.[5]

CASE

We present a case of a 66-year-old male who presented with postprandial abdominal heaviness and symptoms of reflux esophagitis. The patient volunteered history of being a former smoker, with 41 pack years. He reported a history of tonsillectomy in childhood and was only using atorvastatin at the time of presentation with no prior or recent use of anticoagulants. There was no history of any known allergies or trauma reported by the patient.

Abdominal CT ***(Figure 1)***showed a left adrenal mass measuring slightly over 7cm in widest diameter, with some internal areas of calcification. Adjacent to this mass was a small old retroperitoneal hematoma. The rest of the abdominal organs were normal on imaging.

On examination he had a soft and depressible abdomen with tender hepatomegaly noted.
He was admitted urgently due to abdominal pain, perspiration, and mild coldness of the extremities. He underwent surgery a few hours later for what was clinically diagnosed as an adrenal tumor. The patient was stable post-operatively and did not require any further intervention. We followed him up for 2 months.

The macroscopic details of the resected specimen are seen in***Figure 2.***The histopathology description follows in ***Figure 3.***

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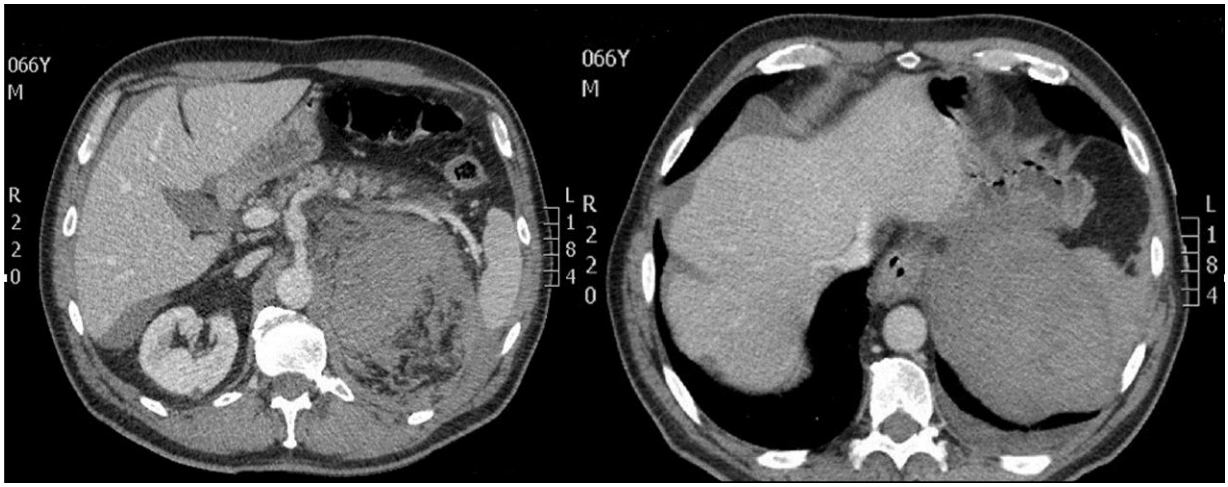

FIGURE 1. Left adrenal mass measuring approximately 7.2 x 6.3cm with internal calcification.
Adjacent to this mass superiorly is a higher density area likely corresponding to a residual encapsulated hematoma, measuring 8cm in its greatest axis in contact with the spleen.
No free intraperitoneal fluid observed. Liver, gall-bladder, biliary tract, Kidneys, Pancreas and Spleen show no significant findings.

FIGURE-2. The specimen submitted for histopathology was an irregular cystic-solid mass of tissue measuring 62 x 57 x 49mm with a total weight of 52g and rubbery in consistency. The surface was variegated with yellow-brown areas distinct from normal fat. The cavity of the mass was formed by a

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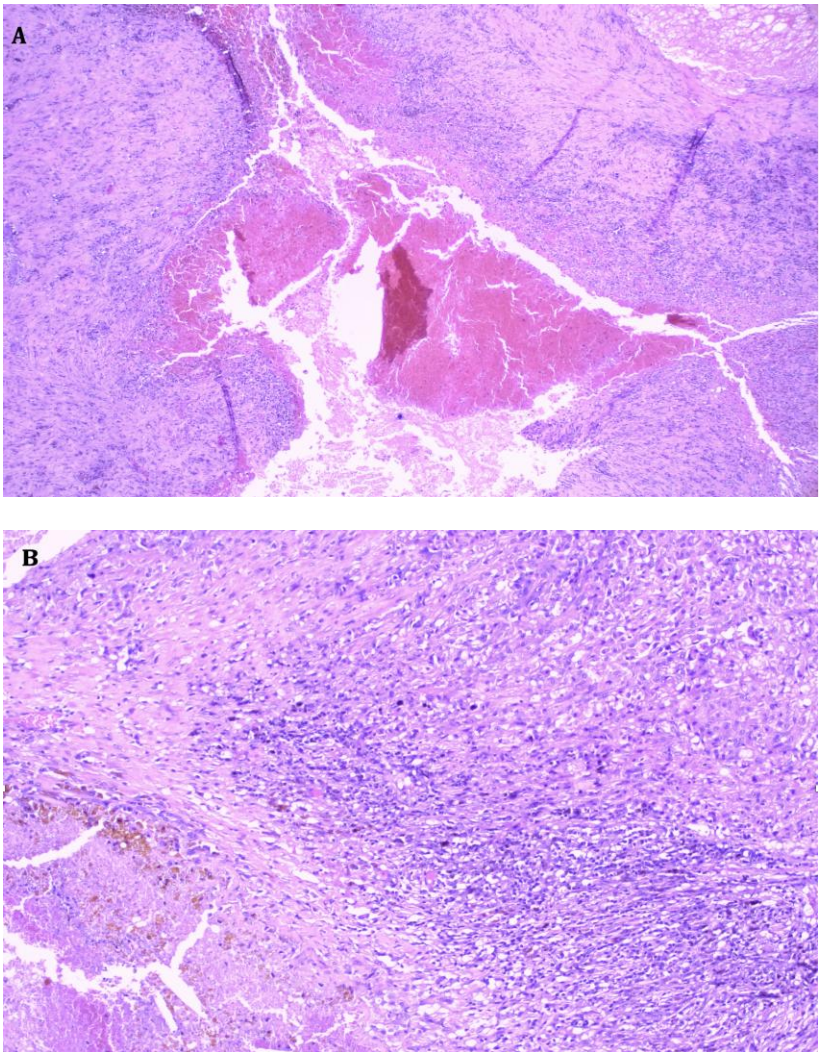
large hematoma with a prominent tract identified along the area with the probe. No single neoplastic nodule was identified.



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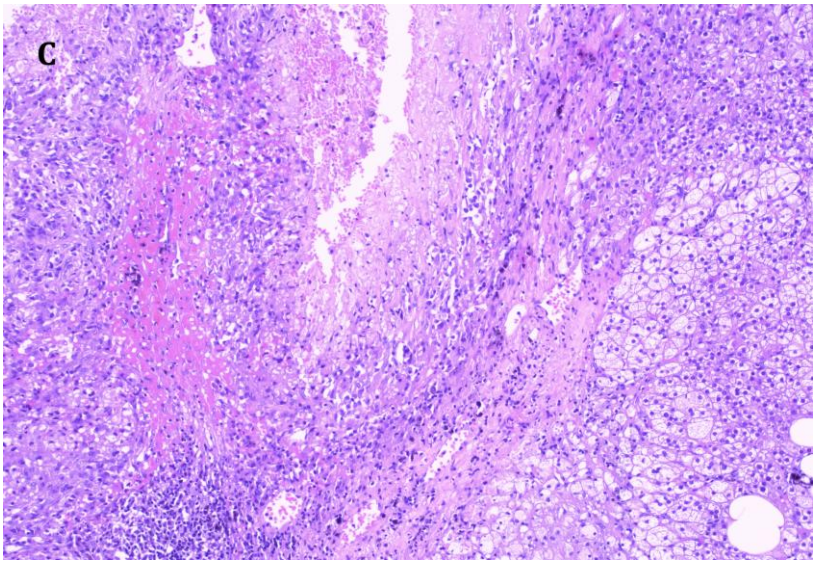

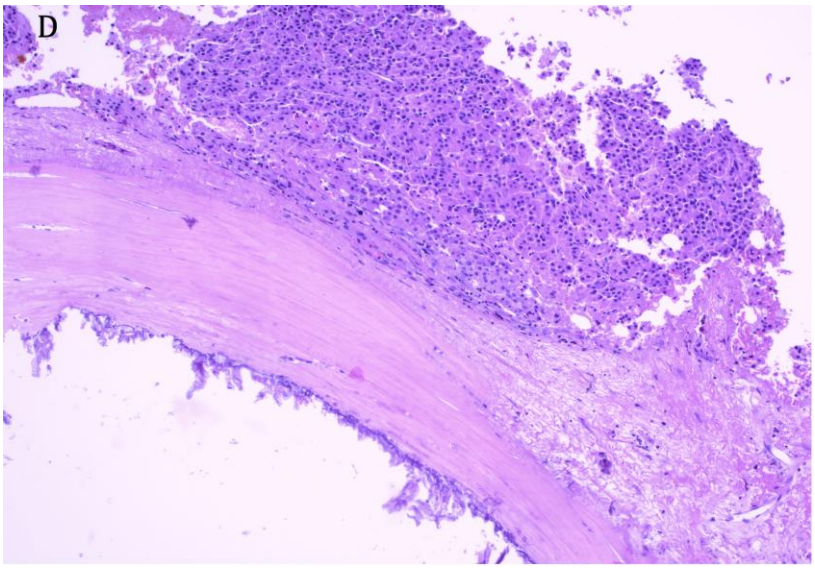

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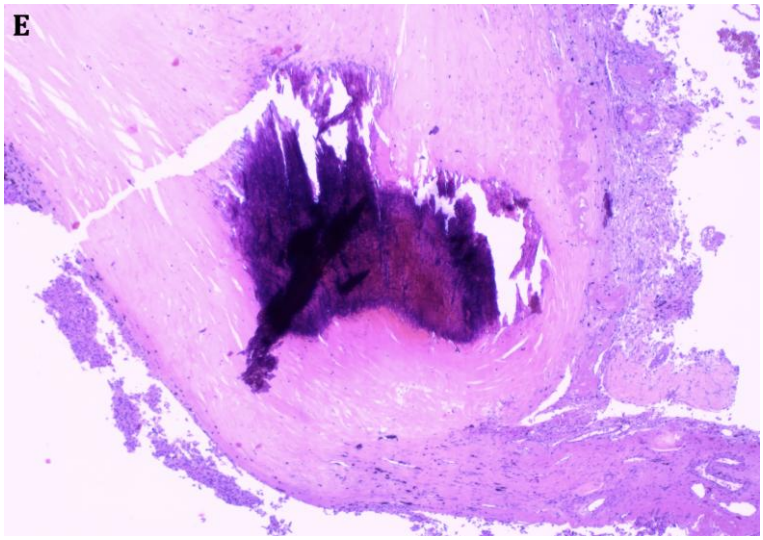

FIGURE 3. Histopathology (A, B, C, D, E)
Histopathology evaluation of the mass showed an adrenal gland with extensive architectural distortion and large central cystic cavity with no epithelial or endothelial lining. (A). Granulation tissue with pigmented histiocytes layered the inner surface of the cystic. Except in the areas of rupture, a thick sclerotic reactive fibrous capsule walled off this cavity contained blood, inflammatory cells, cholesterol cleft (B). The inflammation and hemorrhage extended beyond the adrenal gland into perirenal soft tissue. The adrenal gland showed nodular sclerosis within which entrapped adrenocortical cells were seen. Numerous organizing hematomas were also identified within an ecstatic vascular network. No neoplastic process-bening or malignant, primary or metastatic was seen (C, D, E

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DISCUSSION

As with many other reported cases in the literature, our patient, a middle aged male, presented with hemodynamic instability that required emergency surgical intervention.[1] Hypovolemic shock forms a critical component of the Lenk's triad, a classical presentation of WS which also includes flank pain and a palpable abdominal mass. Our patient did not present with all the features of this triad however this is not unusual and similar cases have been reported by other writers.[10]

Imaging with contrast-enhanced CT scan accurately diagnosed perirenal hemorrhage and the extent of bleeding, although the exact diagnosis of the radiographically confirmed adrenal mass remained a question to be addressed by diagnostic histopathology.

Following initial clinical and imaging assessment, a neoplastic etiology was highly suspected, in keeping with the wider evidence supporting neoplasms as that main cause of peri-renal hemorrhage.[21]Microscopic evaluation however revealed a benign complicated hemorrhagic adrenal mass that had ruptured and induced an extensive tissue response with disruption of the normal architecture of the left adrenal gland and involvement of the perirenal soft tissues.

Considerably fewer cases of adrenal masses have been reported by some as extremely rare causes of perirenal hemorrhage. Among these, myelolipomas and pseudocysts have been the more commonly identified causes of WS, highlighting adrenal lesions as pathologies warranting further investigation and appropriate documentation in the work-up of WS.[3,19,22]

The patient did not develop any immediate or long-term complications following surgery and has had a good prognosis post-operatively which is a commonly reported outcome in patients with Wunderlich syndrome who receive accurate immediate clinical attention.

Over the years since the 1800's, nearly1000 cases of Wunderlich syndrome have been reported to-date.[8]Ourunderstanding of WS has evolved substantially with increasing recognition that causes other than renal masses are of similar clinical significance and multidisciplinary approaches offer superior outcomes in the management of this rare clinical emergency.[23]

Hemodynamic instability requiring urgent intervention has been cited as a common presentation among patients with Wunderlich syndrome and the acute presentation in our patient was no different.[24,25]

While AML is the most common etiology, followed by RCC and renal cysts, cases arising from adrenal masses are of equal clinical significance and remain scant in the literature.[18]This underscores the need for accurate documentation of findings in each case presenting as atraumatic spontaneous subcapsular or perirenal space hemorrhage.

From a clinical diagnostic perspective, CT scan remains an indispensable imaging modality for rapid and accurate evaluation of bleeding, however tissue confirmation ensures accurate

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etiologic classification and prevents misdiagnosis.[12]

Histopathology is central to diagnostic confirmation ofthe presence and nature of neoplastic and non-neoplastic diagnostic entities and distinguishing benign and malignant disease processes, information which is extremely helpful in guiding clinical decision making.[20]

WS exemplifies the importance of clinicopathological correlation in acute adrenal conditions emphasizing the significance of timely and accurate diagnosis which is pivotal to any further treatments following immediate emergency care. Interventional radiology has transformed WS management by reducing nephrectomy rates and improving outcomes with minimally invasive techniques.[1,10]

Areas of future research should include comparative epidemiological data, standardized diagnostic and management algorithms, risk stratification for all causes of WS, histopathological correlates and long-term outcomes following minimally invasive interventions.

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CONCLUSION

Wunderlich syndrome remains a rare and significant entity at the intersection of radiology, urology, and pathology. While renal masses remain the main cause, vasculopathies, coagulopathies and adrenal masses are also important etiologies. CT is still the preferred method for evaluation of perirenal hemorrhage even though its sensitivity for detection of underlying etiology is low. Histopathologic evaluation not only identifies the underlying cause but also directs patient management and prognostication by providing a definite diagnosis. Multidisciplinary collaboration ensures holistic and focused patient management which improves patient outcomes tremendously. Case registries integrating clinical, imaging, and histopathological data should include adrenal etiologies in Wunderlich Syndrome which will be valuable resources that will refine evidence-based clinical practice guidelines.

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