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A Rare Case of Urinary Bladder Hamartoma Clinically Mimicking an Urothelial Carcinoma: A Case Report and Review of the Literature

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Abstract

Urinary bladder hamartoma is a rare benign proliferation with only 14 cases reported in the literature at present. Urinary bladder hamartoma is composed of a disorderly admixture of normal urinary bladder components, essentially represented by glands lined by transitional epithelium and a variable percentage of fibrous stroma, smooth muscle bundles, and adipose tissue. Urinary bladder hamartomas do not exhibit cytological or architectural abnormalities and show no necrosis or increase in mitotic activity. Clinical manifestations are usually represented by lower urinary tract symptoms, more or less frequently paired with gross hematuria. Several pediatric cases of urinary bladder hamartoma have been reported, sometimes with syndromic associations. Transurethral resection has been curative in all cases reported, with no evidence of recurrence. Here we report an additional rare urinary bladder hamartoma, clinically mimicking urothelial carcinoma, providing a review of the literature regarding this unusual entity.

Keywords

urinary bladder hamartoma, gross hematuria, uropathology

Introduction

The term "*hamartoma*" originally introduced by Albrecht in 1904,[1] refers to a benign, although "tumor-like" exaggerated proliferation of elements that recapitulates the normal components of the tissue in which the hamartoma arises.[2] Among various sites where hamartomas have been described in the literature, urinary bladder localization is extremely rare, with only 14 reports in the literature (see Table 1).

Here we describe an additional case of urinary bladder hamartoma, clinically interpreted at first as urothelial carcinoma, and we provide a detailed revision of the published literature regarding this rare entity.

Case Presentation

A 54-year-old woman with type IV Loeys-Dietz syndrome was admitted to the Nephrology Unit of our Institution for rapid onset of left flank pain with gross hematuria and elevated inflammatory markers, suspicious for left pyelonephritis. Past medical history revealed a recent aortic dissection, pulmonary emphysema, gastroesophageal reflux, and uterine leiomyomas. During hospitalization, the patient responded well to antibiotic therapy with piperacillin/tazobactam. Angio-computed tomography (CT) excluded the presence of renal infarction, while abdomen CT revealed left kidney alterations consistent with pyelonephritis complicated with renal abscesses. During the diagnostic workup for pyelonephritis, abdomen ultrasonography (US) and computed tomography (CT) with contrast revealed an 8-millimeter-wide vegetation located on the left posterior wall of the urinary bladder, which exhibited mild contrast enhancement. The lesion was considered to be at least suggestive of urothelial carcinoma. Urine cytology was negative for neoplastic cells. After acute pyelonephritis resolution, the

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Table 1. A Systematic Review of Urinary Bladder Hamartoma Published Cases to Date.

Authors	Year	Reference	Sex	Age	Localization	Clinical presentation	Cytology	IHC	Molecular studies	Therapy	Outcome	Follow-up (months)
Lathan T. Moose and Fred K. Garvey	1963	[3]	M	13	Left posterior wall with trigone extension	Gross hematuria and pyuria	NA	NA	NA	Transurethral resection	No recurrence	60
Borski AA.	1970	[4]	M	45	Bladder neck	LUTS	NA	NA	NA	Transurethral resection	No recurrence	6
Keating MA, Young RH, Lillehei CW, Retik AB	1987	[5]	F	4	Posterior wall	Recurrent urinary tract infections in Peutz-Jeghers syndrome	NA	NA	NA	Partial cystectomy	No recurrence	4
Park C, Kim H, Lee YB, Song JM, Ro JY	1989	[6]	F	45	Bladder dome	LUTS	NA	NA	NA	Transurethral resection	NA	NA
Williams MP, Ibrahim SK, Rickwood AM.	1990	[7]	M	0.8	Posterior wall	Hematuria associated with Beckwith-Wiedemann syndrome	NA	NA	NA	Transurethral resection	No recurrence	18
McCallion WA, Herron BM, Keane PF.	1993	[8]	M	41	Trigone	LUTS associated with hematuria	NA	NA	NA	Transurethral resection	No recurrence	60
Duvenage GF, Dreyer L, Reif S, Bornman MS, Steinmann CF.	1997	[9]	M	19	Right posterior wall	Hematuria associated with schistosomiasis	NA	Muscular immunostains negative	NA	Transurethral resection	No recurrence	5
Ota T, Kawai K, Hattori K, Uchida K, Akaza H, Harada M	1999	[10]	F	58	Left posterior wall, with an invasive appearance at imaging	LUTS	No malignant cells	NA	NA	Transurethral resection followed by partial cystectomy	No recurrence	36
Brancatelli G, Midiri M, Sparacia G, Martino R,	1999	[11]	M	30	Right posterior wall, with intramural	Gross hematuria, fever	NA	NA	NA	Partial cystectomy	No recurrence	12

(continued)

Table 1. (continued)

Authors	Year	Reference	Sex	Age	Localization	Clinical presentation	Cytology	IHC	Molecular studies	Therapy	Outcome	Follow-up (months)
Rizzo G, Lagalla R					extension at imaging							
Adam A, Gayaparsad K, Engelbrecht MJ, Moshokoa EM	2013	[12]	M	5	Trigone	LUTS associated with Goldenhar syndrome	NA	NA	NA	Transurethral resection	No recurrence	2
Pieretti A, Wu CL, Pieretti RV.	2014	[13]	M	0.2	Anterior wall	Prenatal detection	NA	S100−, HMB45−, keratin−, SMA+	NA	Transurethral resection	No recurrence	18
Murray C, Marchan J, Özel B, Özel B.	2015	[14]	F	51	Bladder neck	LUTS	NA	NA	NA	Transvaginal excision	No recurrence	2
Al Shahwani N, Alnaimi AR, Ammar A, Al-Ahdal EM	2016	[15]	M	15	Left lateral wall	LUTS	NA	NA	NA	Transurethral resection	No recurrence	NA
Kumar, J, Albeerdy, MI, Shaikh, NA et al	2021	[16]	M	20	Bladder neck	LUTS in Peutz-Jeghers syndrome	NA	NA	NA	Transurethral resection + intravesical mitomycin	NA	NA
Present case	2022		F	54	Posterior left wall	Incidental finding	No malignant cells	keratin8/18+, EMA+, p63+, keratin7+/−, PAX8−	NA	Transurethral resection	NA	NA

Abbreviations: NA, not assessed; LUTS, lower urinary tract symptoms; EMA, epithelial membrane antigen.

patient underwent a cystoscopy that revealed an oval and pedunculated formation located between the trigone area and the left posterior wall, which was therefore excised by transurethral resection to exclude malignancy. At histopathological examination (Figure 1), the lesion revealed a sessile/nodular silhouette and was composed of an admixture of tubules and cystically dilated glands lined by mono- or pseudostratified urothelium and containing eosinophilic proteinaceous material, with no architectural nor cytological atypia. The tubulo-glandular elements were dispersed within a fibrotic stroma with scattered smooth muscle bundles, numerous plump fibroblasts, and increased vessel density. No necrosis nor mitotic activity was observed. Immunohistochemistry (Figure 2) revealed strong positivity for keratin 8/18, epithelial membrane antigen (EMA), keratin AE1/AE3, and p63, negativity for PAX8 and

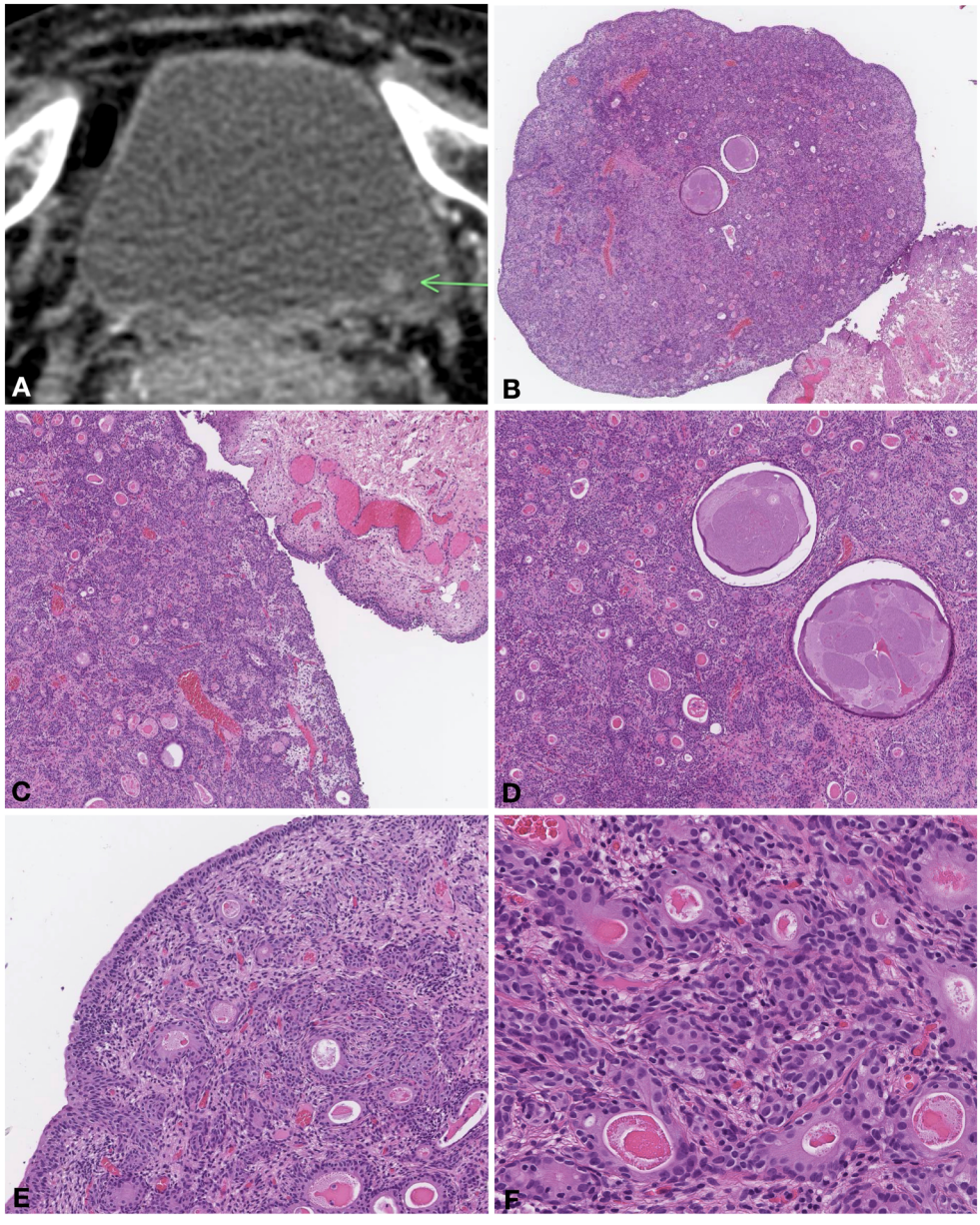

Figure 1. Contrast CT revealed an 8-millimeter-wide vegetation located on the left posterior wall of the urinary bladder (A, arrow). The lesion showed a nodular silhouette (B, H&E stain, 4× magnification) and was composed of tubulo-glandular structures, often cystically dilated, lined by a single or stratified urothelium and filled with proteinaceous material, in a background of fibrotic stroma with congested capillaries, scattered smooth muscle bundles and plump fibroblasts (C-D, H&E stain, 10× magnification; E, H&E stain, 20× magnification; F, H&E stain, 40× magnification).
Abbreviations: H&E, hematoxylin and eosin; CT, computed tomography.

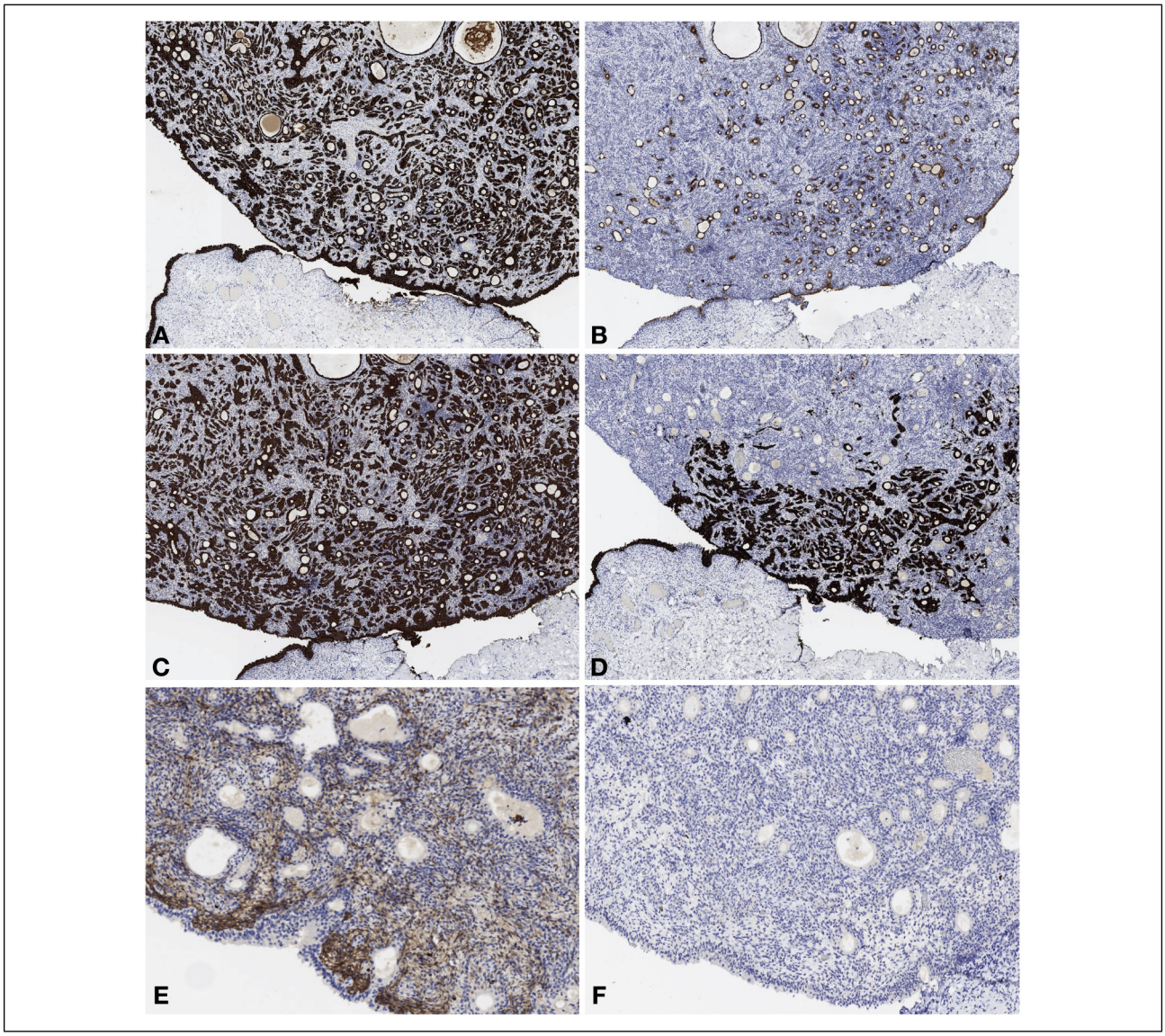

Figure 2. Hamartoma urothelium reveals strong positivity for keratin AE1/AE3 (A, 10× magnification), EMA (B, 10× magnification), and keratin 8-18 (C, 10× magnification), focal expression of keratin 7 (D, 10× magnification) and negativity for CD10 (E, 20× magnification) and PAX8 (F, 20× magnification).

CD10, and faint/focal expression of keratin 7. The proliferative index, evaluated with MIB1/Ki67 antibody, was extremely low (< 1%).

Telomerase reverse transcriptase (*TERT*) promoter mutation analysis, performed with the Amoy Diagnostics® kit, revealed a wild-type configuration, arguing against an urothelial carcinoma diagnosis altogether with the above-mentioned features.

Given these findings, a urinary bladder hamartoma diagnosis was made.

Discussion

To systematically review the published literature regarding urinary bladder hamartoma, we performed a PubMed search using the terms: "urinary bladder hamartoma" and "bladder hamartoma," which showed 89 results. Of these, 14 were reports of urinary bladder hamartoma, for a total of 15 individual cases (the present included), whose clinicopathological characteristics are summarized in Table 1. The very first bladder hamartoma reported by Davis in 1949[17] was subsequently diagnosed as urinary bladder nephrogenic adenoma and was therefore excluded from our revision.

Most reported hamartomas affected male patients (10/15; 67%) with a male-to-female ratio of 2 and a mean age at diagnosis of 30 years. Bladder posterior wall was the most common localization (7/15, 47%), followed by bladder neck (3/15, 20%), trigone (2/15, 13%), anterior wall (1/15, 6.7%), left lateral wall (1/15, 6.7%), and bladder dome (1/15, 6.7%).

Clinical features were represented by irritative lower urinary tract symptoms with or without gross hematuria (8/15, 53%); gross hematuria alone was observed in 27% of patients (4/15). One case was associated with urinary bladder schistosomiasis,[9] while another one was the subject of an *in-utero prenatal* diagnosis.[13] Interestingly, 33% of lesions (5/15), including the present one, arose in the context of specific syndromes, such as Peutz-Jeghers syndrome,[5,16] Beckwith-Wiedemann syndrome,[7] Goldenhar syndrome,[12] and, in our patient, Loeys-Dietz syndrome (LDS). LDS is an autosomal dominant connective disorder characterized by systemic involvement, mainly due to transforming growth factor beta (*TGFB*) ligand or receptor mutations. LDS encompasses craniofacial, skeletal, cutaneous, and vascular abnormalities, partly overlapping with Marfan syndrome manifestations: distinguishing LSD features are cleft palate/bifid uvula, hypertelorism, and arterial tortuosity. LSD is divided into 5 subtypes defined by different molecular alterations, with type IV LSD specifically bearing *TGFB2* mutations and showing a milder phenotype.[18,19] To the best of our knowledge, no association of hamartomas with LSD has been reported to date.

All lesions shared a common architectural and morphologic appearance: a lobulated mass composed of a mixed proliferation of tubulo-glandular, nested, or even papillary epithelial components intermingled with smooth muscle bundles, fibromyxoid stroma with plump fibroblasts, and sometimes adipose tissue. The nested or tubule-glandular elements were often cystically dilated, lined by a single or stratified urothelium with no atypia, and filled with proteinaceous material, resembling florid von Brunn nest hyperplasia or cystitis cystica glandularis. Intestinal metaplasia and hypervascularity were other potential features observed in these lesions.[10,14-16] No mitoses nor necrosis were observed.

Aside from the present case, immunohistochemical characterization has been performed only on 2 other hamartomas, one which showed negativity of muscular markers[9] and one which was positive for SMA and negative for S100, HMB45, and keratins.[13]

Urine cytology was available only for 2 patients (the present included) and revealed no significant alterations. No molecular data is available regarding urinary bladder hamartomas.

Differential diagnoses of urinary bladder hamartoma may include von Brunn hyperplasia, cystitis cystica glandularis, nephrogenic adenoma, inverted urothelial papilloma, and nested/microcystic variant of urothelial carcinoma, particularly in cases with apparent infiltrative growth at imaging studies.[10,11,20] Differential diagnosis with florid von Brunn hyperplasia and cystitis cystica glandularis might be problematic, although it is not clinically relevant as they all represent benign lesions.[21] Distinguishing features of urinary bladder hamartoma might be represented by the markedly exophytic and lobulated architecture, the presence of plump fibroblasts within the fibromyxoid stroma, and prominent hypervascularity. Florid von Brunn hyperplasia and cystitis cystica glandularis are usually a response to chronic inflammation and irritation, such as prolonged catheterization.[22] Our patient was catheterized during hospitalization; however, the urinary bladder lesion was found concomitantly with pyelonephritis, and we exclude a causative relationship with such a short-term catheterization.

Nephrogenic adenoma is a benign lesion presumably derived from renal tubular cells and related to prior inflammatory insult, which can exhibit a tubular, tubule-cystic, polypoid, and/or papillary growth pattern. Nephrogenic adenoma is composed of tubules of variable size with the basement membrane, luminal eosinophilic secretion, abundant intervening stroma, and cystic dilations. Despite its similarities with urinary bladder hamartoma, nephrogenic adenoma exhibits striking immunohistochemical positivity for AMACR, CD10, PAX8, EMA, keratin 7, and aquaporin-1, while it is negative for p63 and keratin 20.[23–26] Our case exhibited strong p63 positivity and CD10 and PAX8 negativity, thus arguing against a nephrogenic adenoma diagnosis.

Inverted urothelial papillomas are endophytic benign neoplasms that exhibit a pushing growth pattern into the lamina propria. While they usually manifest cystoscopically as raised lesions, their histological examination reveals typical anastomosing urothelial cords of normal thickness with unequivocal endophytic growth and no necrosis, mitotic activity, or cytological atypia. Inverted urothelial papillomas are keratin 20 negative and show a low proliferative index evaluated by means of MIB1-Ki67 expression; their molecular analysis reveals *KRAS* or *HRAS* mutations.[27–30] In our case, architectural and morphological features, paired with the absence of an endophytic growth pattern, were sufficient to exclude an inverted papilloma.

Nested and tubular/microcystic variants of urothelial carcinoma may mimic urinary bladder hamartoma (as well as florid von Brunn nests hyperplasia) due to their nested/microcystic architecture and bland cytology; clear evidence of infiltrative growth is of pivotal importance in the identification of these deceptive variants of urothelial carcinoma. In complex cases, as in superficial biopsies, the identification of *TERT* promoter mutation is of great help in diagnosing malignancy, since it is deemed the most common molecular alteration among urothelial carcinomas.[30-33] Our lesion did not exhibit infiltrative growth nor *TERT* promoter mutations, thus arguing against such a diagnosis. Urinary bladder rhabdomyosarcoma might also be included in the spectrum of radiological differential diagnoses, especially in pediatric patients.[5]

All patients were effectively cured by complete excision via transurethral resection, partial cystectomy, or transvaginal excision; in one instance[16] simultaneous administration of intravesical mitomycin was performed in the suspicion of malignancy. No recurrence of the

disease was reported, even after follow-up periods of up to 60 months.

In conclusion, urinary bladder hamartoma might be the underlying etiologic factor in a small percentage of patients experiencing gross hematuria and/or lower urinary tract symptoms. Urinary bladder hamartoma's radiological and cystoscopic features may sometimes rise suspicion of malignancy. On the other hand, its rarity and benign pathological features, resembling von Brunn nest hyperplasia or cystitis cystica glandularis, might hamper its identification, making it a potentially underdiagnosed condition. Definitive diagnosis mandatorily requires pathological examination and thorough clinical correlation, sometimes, as in our case, with the aid of molecular investigations to exclude malignancy. Of interest, its consistent yet unexplained association with certain syndromic clinical pictures might also be a useful hint for this diagnosis.

Declaration of Conflicting Interests

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Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

Informed Consent

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Trial Registration

Not applicable, because this article does not contain any clinical trials.

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References

1. Ober WB. Selected items from the history of pathology: Eugen Albrecht, MD (1872-1908): hamartoma and choristoma. *Am J Pathol*. 1978;91(3):606.
2. Batsakis JG. Nomenclature of developmental tumors. *Annals of Otology, Rhinology & Laryngology*. 1984;93(1):98-99. doi:10.1177/000348948409300122
3. Lathan T, Moose FKG. Hamartoma of the bladder. *J Urol.* 1963;48(2): 185-187.
4. Borski AA. Hamartoma of the bladder. *J Urol.* 1970;104(5):718-719. doi:10.1016/S0022-5347(17)61819-6
5. Keating MA, Young RH, wL C, Retik AB. Hamartoma of the bladder in a 4-year-old girl with hamartomatous polyps of the gastrointestinal tract. *J Urol.* 1987;138(2):366-369. doi:10.1016/S0022-5347(17)43148-X
6. Park C, Kim H, Lee YB, Song JM, Ro JY. Hamartoma of the urachal remnant. *Archives of Pathology and Laboratory Medicine*. 1989;113(12):1393-1395.
7. Williams MPL, Ibrahim SK, Rickwood AMK. Hamartoma of the urinary bladder in an infant with Beckwith-Wiedemann syndrome. *Br J Urol.* 1990;65(1):106-107. https://doi.org/10.1111/j.1464-410X.1990.tb14671.x
8. McCallion WA, Herron BM, Keane PF. Bladder hamartoma. *Br J Urol.* 1993;72(3):382-383. https://doi.org/10.1111/j.1464-410X.1993.tb00741.x
9. Duvenage GF, Dreyer L, Reif S, Bornman MS, Steinmann CF. Bladder hamartoma. *BJU Int.* 1997;79(1):133-134. https://doi.org/10.1046/j.1464-410X.1997.128832.x
10. Ota T, Kawai K, Hattori K, Uchida K, Akaza H, Harada M. Hamartoma of the urinary bladder. *Int J Urol.* 1999;6(4):211-214. https://doi.org/10.1046/j.1442-2042.1999.06434.x
11. Brancatelli G, Midiri M, Sparacia G, Martino R, Rizzo G, Lagalla R. Hamartoma of the urinary bladder: case report and review of the literature. *Eur Radiol.* 1999;9(1):42-44. doi:10.1007/s003300050624
12. Adam A, Gayaparsad K, Engelbrecht M, Moshokoa E. Bladder hamartoma: a unique cause of urinary retention in a child with Goldenhar syndrome. *Saudi J Kidney Dis Transpl.* 2013;24(1):89-92.
13. Pieretti A, Wu C-L, Pieretti RV. Bladder hamartoma in a fetus: case report. *Urol Case Rep.* 2014;2(5):154-155. https://doi.org/10.1016/j.eucr.2014.06.005
14. Murray C, Marchan J, Özel B, Özel B. Bladder wall hamartoma: an unusual cause of urinary urgency and frequency. *Urogynecology*. 2015;21(1):e8-e10.
15. Al Shahwani N, Alnaimi AR, Ammar A, Al-ahdal EM. Hamartoma of the urinary bladder in a 15-year-old boy. *Turk J Urol*. 2016;42(2):101-103.
16. Kumar J, Albeerdy MI, Shaikh NA, Qureshi AH. Bladder hamartoma in Peutz-Jeghers syndrome: a rare case report. *Afr J Urol.* 2021;27(1):74-74. doi:10.1186/s12301-021-00172-8
17. Davis TA. Hamartoma of the urinary bladder. *Northwest Med*. 1949;48(3):182-185.
18. Gouda P, Kay R, Habib M, Aziz A, Aziza E, Welsh R. Clinical features and complications of Loeys-Dietz syndrome: a systematic review. *Int J Cardiol*. 2022;362:158-167. doi:10.1016/j.ijcard.2022.05.065
19. Velchev JD, Van Laer L, Luyckx I, Dietz H, Loeys B. Loeys-Dietz syndrome. *Adv Exp Med Biol*. 2021;1348:251-264. doi:10.1007/978-3-030-80614-9_11
20. Samaratunga H, Delahunt B, Yaxley J, Egevad L. Tumour-like lesions of the urinary bladder. *Pathology*. 2021;53(1):44-55. doi:10.1016/j.pathol.2020.08.005
21. Volmar KE, Chan TY, De Marzo AM, Epstein JI. Florid von Brunn nests mimicking urothelial carcinoma: a morphologic and immunohistochemical comparison to the nested variant of urothelial carcinoma. *Am J Surg Pathol*. 2003;27(9):1243-1252. doi:10.1097/00000478-200309000-00008

22. Magied A, Badreldin MH, Leslie AM, W S. Cystitis Cystica. *StatPearls*. StatPearls Publishing.
23. Mazal PR, Schaufler R, Altenhuber-Müller R, et al. Derivation of nephrogenic adenomas from renal tubular cells in kidney-transplant recipients. *N Engl J Med*. 2002;347(9):653-659. doi:10.1056/NEJMoa013413
24. Amin W, Parwani AV. Nephrogenic adenoma. *Pathology - Research and Practice*. 2010;206(10):659-662. https://doi.org/10.1016/j.prp.2010.06.001
25. Turcan D, Acikalin MF, Yilmaz E, Canaz F, Arik D. Nephrogenic adenoma of the urinary tract: a 6-year single center experience. *Pathol Res Pract*. 2017;213(7):831-835. doi:10.1016/j.prp.2017.03.001
26. Tong GX, Weeden EM, Hamele-Bena D, et al. Expression of PAX8 in nephrogenic adenoma and clear cell adenocarcinoma of the lower urinary tract: evidence of related histogenesis? *Am J Surg Pathol*. 2008;32(9):1380-1387. doi:10.1097/PAS.0b013e31816b1020
27. Picozzi S, Casellato S, Bozzini G, et al. Inverted papilloma of the bladder: a review and an analysis of the recent literature of 365 patients. *Urol Oncol*. 2013;31(8):1584-1590. doi:10.1016/j.urolonc.2012.03.009
28. McDaniel AS, Zhai Y, Cho KR, et al. HRAS mutations are frequent in inverted urothelial neoplasms. *Hum Pathol*. 2014;45(9):1957-1965. doi:10.1016/j.humpath.2014.06.003
29. Sweeney MK, Rais-Bahrami S, Gordetsky J. Inverted urothelial papilloma: a review of diagnostic pitfalls and clinical management. *Can Urol Assoc J*. 2017;11(1-2):66-69. doi:10.5489/cuaj.4136
30. *WHO Classification of Tumors: Urinary and male genital tumours*. 5th ed. vol 8. International Agency for Research on Cancer; 2022.
31. Kurtis B, Zhuge J, Ojaimi C, et al. Recurrent TERT promoter mutations in urothelial carcinoma and potential clinical applications. *Ann Diagn Pathol*. 2016;21:7-11. doi:10.1016/j.anndiagpath.2015.12.002
32. Hayashi Y, Fujita K, Netto GJ, Nonomura N. Clinical application of TERT promoter mutations in urothelial carcinoma. *Front Oncol*. 2021;11:705440. doi:10.3389/fonc.2021.705440
33. Wasco MJ, Daignault S, Bradley D, Shah RB. Nested variant of urothelial carcinoma: a clinicopathologic and immunohistochemical study of 30 pure and mixed cases. *Hum Pathol*. 2010;41(2):163-171. doi:10.1016/j.humpath.2009.07.015