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Original Article

Bladder xanthoma: clinical analysis of 22 cases from multiple centers

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Abstract: This study aims to outline the clinical and pathological characteristics of bladder xanthoma, alongside its diagnostic and treatment approaches. Methods: We reviewed bladder xanthoma literature spanning the last 60 years from databases such as PubMed, Web of Science, Embase, and Medline. Additionally, we analyzed clinical data from a singular case of bladder xanthoma treated at our hospital. Patient particulars, including age, gender, symptoms, tumor size, associated neoplasms, imaging results, and pathological findings, were documented. Tumors underwent surgical removal, followed by pathological examination of the excised tissues. Subsequent to surgery, patients underwent cystoscopy follow-up after 3 months. Results: Among the 22 identified cases of bladder xanthoma, 15 were solitary (comprising both single and multiple lesions), while 7 were associated with urinary tract epithelial tumors. There were 6 male patients and 1 female patient concurrently diagnosed with urinary tract epithelial carcinoma. Males exhibited an average onset age of 56.0 years, with an average tumor diameter of 21.57 mm. Females presented an average onset age of 63.00 years, with an average tumor diameter of 20.86 mm. The onset age for females was notably lower than that for males, and their tumor diameter was significantly smaller than that of males ($P<0.05$). Among the 9 patients with lipid metabolism disorders, 7 were males and 2 were females, indicating a marked male predominance. No instances of recurrence or malignant transformation were observed during follow-up. In this study, we treated a 65-year-old female patient who, during cystoscopy, exhibited a round, hanging lesion measuring about 2.5 × 1 × 1 cm on the left side of the ureteral opening in the bladder trigone. Post-surgery, pathological examination disclosed bladder xanthoma with multiple groups of foam cells. Immunohistochemistry findings were as follows: CD68 (+), CD163 (+), Vimentin (+), CK (-), Desmin (-). A follow-up cystoscopy after 3 months did not reveal any tumor recurrence. Conclusion: Bladder xanthoma is an uncommon benign condition predominantly affecting older males. It frequently manifests on the side walls and trigone region of the bladder and may be linked to lipid metabolism disorders. Approximately 50% of patients exhibit concurrent urinary tract epithelial tumors, with diagnosis primarily reliant on microscopic tissue examination. Prolonged post-surgical follow-up is imperative.

Keywords: Bladder xanthoma, hypercholesterolemia, urinary tract epithelial tumor

Introduction

Xanthoma, a benign condition resulting from the localized accumulation of lipid-filled foam cells in the mucosal layer, typically presents as yellowish changes on the skin or mucous membranes, with a higher prevalence on the skin, tendons, and gastrointestinal tract. However, its occurrence in the bladder is exceptionally rare. While clinical evidence suggests an association with elevated cholesterol levels, there is a lack of definitive research and substantial clinical data. Some experts have even suggested that xanthomas could develop in individuals with normal lipid metabolism [1].

Bladder xanthoma, an infrequent phenomenon within the bladder region, is a rare condition mainly linked to hyperlipidemia. In certain cases, local lipid metabolism disorders triggered by surgery, trauma, or inflammatory stimulation in the lesion area result in the aggregation of foam cells. Most patients with bladder xanthoma exhibit no overt symptoms, and a few may display microscopic hematuria, urinary tract infection, and other symptoms, which can

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be easily mistaken for malignant bladder tumors. Diagnosis primarily relies on pathology, characterized by the accumulation of macrophages and foam cells in the tissue lamina propria, without multinucleated cells. The first documented case was reported by Miliauskas et al. [2] in 1992, with a total of 32 cases documented since then. Due to its limited occurrence, comprehensive analysis and research on this condition are lacking. Additionally, bladder xanthoma often coexists with urinary tract epithelial cancer, leading to potential misdiagnosis, unnecessary examinations, and unwarranted treatments during clinical management. Therefore, this study aims to consolidate data from 22 reported cases of bladder xanthoma across various medical centers, along with information from 2 cases treated at our institution. The objective is to summarize its incidence patterns, clinical symptoms, signs, imaging features, pathological characteristics, and provide a reliable foundation and practical treatment approach for the clinical diagnosis and management of bladder xanthoma.

Materials and methods

Search strategy

A comprehensive search spanning nearly 60 years was undertaken, utilizing keywords such as "Xanthoma of bladder" in databases like PubMed, Web of Science, and Chinese databases. All eligible case reports and series studies were included in this investigation.

Inclusion criteria and exclusion criteria

Studies with pathologically confirmed bladder xanthoma as subjects, with or without an associated urothelial neoplasm, were retrieved. Urological pathologists reviewed all haematoxylin and eosin (H&E)-stained slides to confirm the diagnosis. Literature related to conditions such as xanthogranulomatous cystitis and bladder inflammation was excluded.

Outcome indicators

Clinical information was gathered from patients with pathologically confirmed bladder xanthoma, encompassing fundamental details, clinical manifestations, results of additional tests, pathological findings, treatment specifics, and assessments of lipid metabolism and co-existing urinary tract epithelial carcinoma. Medical records from our hospital were also selected for a confirmed bladder xanthoma case, including onset age, symptoms, signs, and supplementary examinations. The patient underwent transurethral resection of the bladder tumor, followed by immunohistochemistry and HE staining for the pathological analysis of excised tissues. A follow-up examination and cystoscopy were performed after 3 months to monitor potential recurrence.

Statistical analysis

Clinical information was gathered from patients for statistical analysis using SPSS 20 software. The two-dimensional percentage chart was generated using Graphpad Prism 8 software. Percentages were employed to express categorical data, and data comparisons were conducted using χ^2 inspection.

Results

Epidemiological characteristics of bladder xanthoma

Following data identification, screening, and eligibility assessment, a total of 22 studies were systematically reviewed and included in the analysis (**Figure 1**). The review covered 22 cases of bladder xanthoma, with detailed case characteristics outlined in **Table 1**. Baseline information, clinical presentations, lipid metabolism, cystoscopy findings, and associated tumor status are presented in **Table 2**. Among the cases, 15 males and 7 females were identified, resulting in a male-to-female ratio of 2.1:1. The average age was 60.8 years (range: 34-80 years), with a mean tumor diameter of 21 mm (range: 3-100 mm). Seven cases were concomitant with low-grade urinary tract epithelial tumors, and 9 cases exhibited metabolic irregularities (hyperlipidemia) (**Figures 2**, **3**). Males had an average onset age of 56 years, with an average tumor diameter of 21.57 mm. In contrast, females had an average onset age of 63.00 years, with an average tumor diameter of 20.86 mm. The onset age for females was notably lower than that for males, and their tumor diameter was significantly smaller ($P<0.05$). Among the 9 patients with metabolic irregularities, 7 were males and 2 were females, with males predominantly presenting elevated cholesterol levels. Seven patients had co-exist-

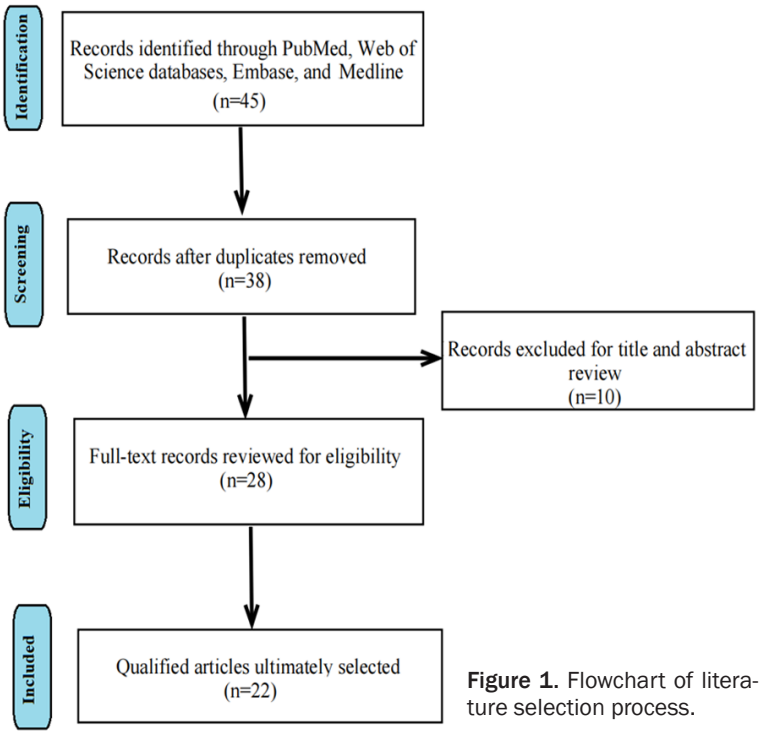

Figure 1. Flowchart of literature selection process.

Table 1. Demographic and clinicopathological characteristics of patients

	Total (22)	Percentage (%)
Gender		
Male	15	68.2%
Female	7	31.8%
Age		
<40	2	9%
41-50	4	18.3%
51-60	3	13.7%
61-70	7	31.8%
>70	6	27.2%
Hyperlipidemia		
Yes	9	45.50%
No	13	54.50%
Tumor location		
Left wall	6	27.2%
Trigone	2	9.1%
Right wall	4	18.2%
Dome of the bladder	6	27.2%
Posterior wall	4	18.1%
Tumor diameter		
<1 cm	10	45.4%
1-2 cm	7	31.8%
>2 cm	5	13.7%
With urothelial tumor		
Yes	17	53%
No	15	47%

ing urinary tract epithelial tumors, including 6 males and 1 female diagnosed with a urinary tract papillary tumor at the age of 80.

Clinical and pathological characteristics of bladder xanthoma

Patients with bladder xanthoma often lack significant clinical symptoms. Those with concurrent urinary tract epithelial tumors primarily exhibit hematuria and bladder irritation symptoms. Some patients were incidentally detected during cystoscopy or routine medical assessments. Cystoscopy reveals velvety or patchy yellowish lesions resembling a swan-down-like texture or nodules, occasionally presenting as multiple nodules. Pathological biopsies show focal accumulations of foam-like lipid cells and macrophages in the epithelial lamina propria, with no infiltration of acute or chronic inflammatory cells, multinucleated cells, or other cell types. Following diagnosis, all patients underwent surgical excision treatment, and postoperative follow-up averaged 9 months (range: 4-18 months). No instances of recurrence or malignant transformation were observed (**Table 2**).

Case report

A single female participant, aged 65, was included in this study, presenting with challenging urination, a slender urinary stream, and noticeable gross hematuria resembling wash water interspersed with sporadic blood clots. A urinary system color Doppler ultrasound identified right kidney hydronephrosis and multiple solid intravesical lesions.

Table 2. Summary of published reports on patients with isolated bladder xanthomas

Author	Publication time	Gender	Age (years)	Clinical presentation	Metabolic abnormality	Surgical method	Location	Max. size (cm)	Associated neoplasm
SCHOLL AJ [13]	1945	Male	59	Hematuria	Hyperlipidemia	Partial ystectomy	Left wall	40	LGUC (Ta-G1)
Miliauskas JR [2]	1992	Male	79	Cystoscopic control	NA	TURBT	Right of the trigone	5	LGUC (T1-G2)
Nishimura K [4]	1994	Male	61	Lower abdominal pain	Hyperlipidemia	TURBT	Left wall	10	NA
Toda F [14]	1997	Male	68	Microscopic hematuria	NA	Cystectomy	Dome of the bladder	100	NA
Skopelitou A [5]	2000	Male	65	Hematuria, dysuria and lower abdominal pain	Hyperlipidemia	TURBT	Trigone	20	NA
S V Chitale [15]	2002	Male	63	Macroscopic Haematuria and passage of debris per urethra	NA	TURBT	Posterior wall	15	NA
Hayashi N [16]	2003	Female	70	Postmicturition pain	Hyperlipidemia	Partial ystectomy	Dome of the bladder	60	NA
Kobayashi F [3]	2004	Male	55	Macrohematuria	NA	TURBT	Left wall	3	NA
Martí Mestre J [17]	2004	Male	80	Other	NA	TURBT	Posterior wall	20	LGUC (Ta-G1)
Lindboe CF [18]	2005	Female	78	Cystoscopic control	NA	TURBT	Right wall	4	LGUC (T2-G2)
Al-Daraji WI [11]	2007	Female	74	Urinary frequency	Hyperlipidemia	TURBT	Dome of the bladder	5	NA
Al-Daraji WI [11]	2007	Male	53	Microscopic haematuria	NA	TURBT	Dome of the bladder	10	NA
Fornari A [19]	2007	Male	67	Hematuria	Hyperlipidemia	Partial ystectomy	Dome of the bladder	60	LGUC (T2-G3)
Yang KS [20]	2011	Male	41	Hematuria	NA	TURBT	Posterior wall	10	NA
Vimal M [21]	2012	Female	46	Urgency and incontinence	NA	TURBT	Dome wall	5	NA
Hassouna H [7]	2014	Male	77	Elevated PSA	NA	TURBT	Left wall	5	NA
Raghavendran M [8]	2016	Male	34	Flank pain	Hyperlipidemia	TURBT	Left wall	5	NA
Shah SJ [22]	2017	Female	38	Lower abdominal pain		Partial ystectomy	Right wall	60	NA
Piol N [6]	2018	Male	75	Macrohematuria	Hyperlipidemia	TURBT	Right wall	5	LGUC (Ta-G2/G3)
Piol N [6]	2018	Male	68	Macrohematuria and acute urinary retention	Hyperlipidemia	TURBT	Posterior wall	5	LGUC (T1-G3)
Jain K [10]	2023	Male	55	Hematuria, dysuria and lower abdominal pain	NA	TURBT	Right wall	14	NA
Yalei Cao [12]	2020	Female	43	Abdominal pain	NA	TURBT	Left wall	3	NA

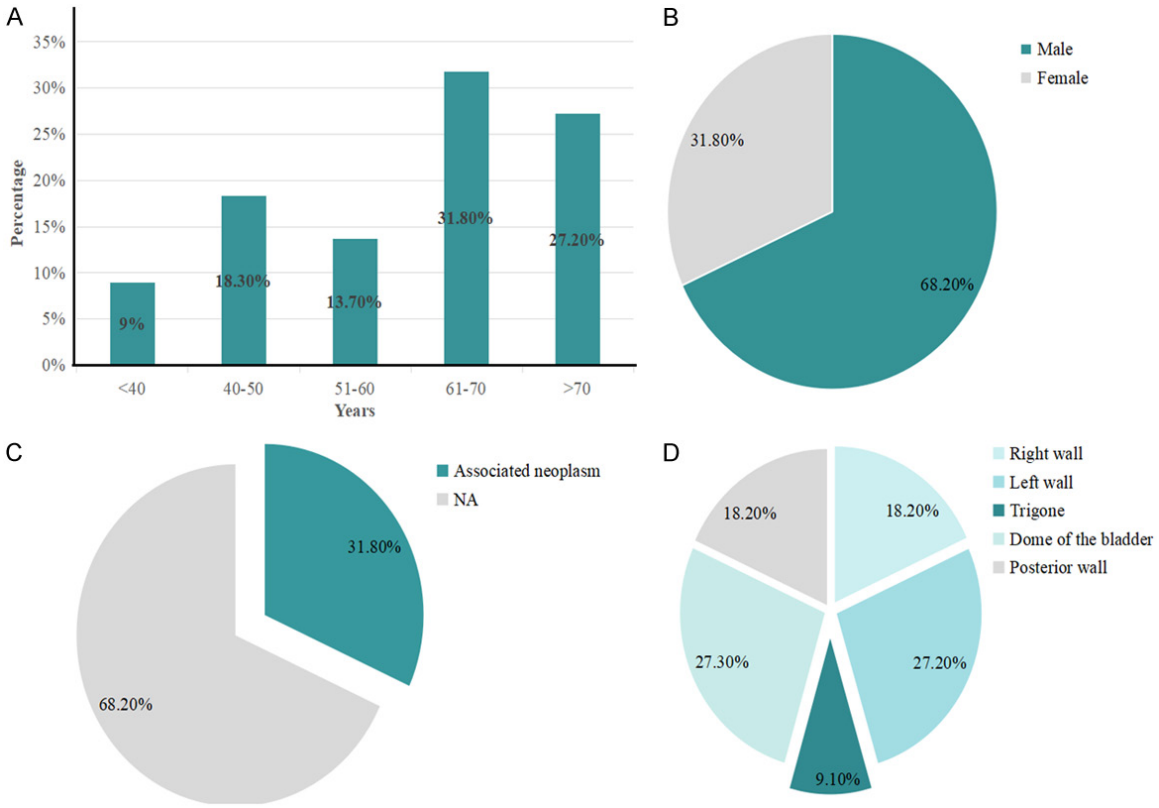

Figure 2. Features of bladder xanthoma. A. Age of patients; B. Gender; C. Features of combined hyperlipidemia; D. Features of location.

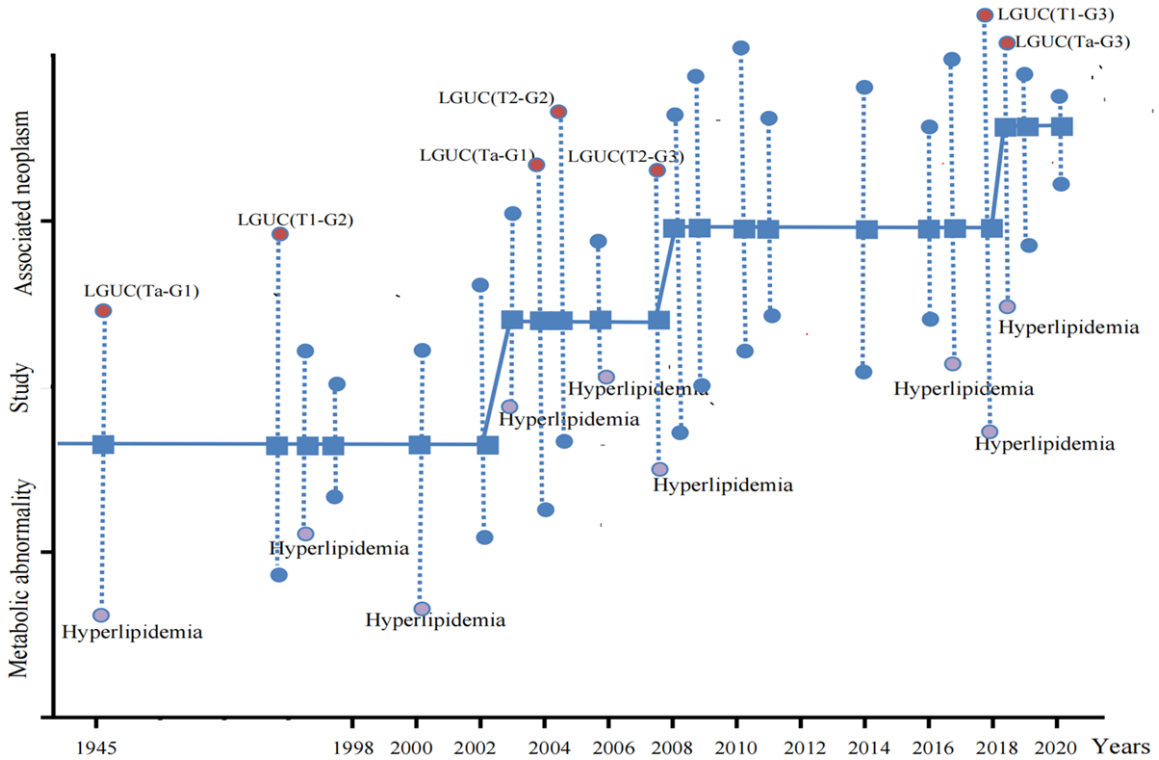

Figure 3. Shifts in the past 60 years of combined hyperlipidemia and LGUC for bladder xanthoma (LGUC: Low Grade Urothelial Carcinoma). The square represents the time node, Red dots represent the merging of LGUC, Blue dots represent no comorbidities, Purple dots represent the merging of hyperlipidemia.

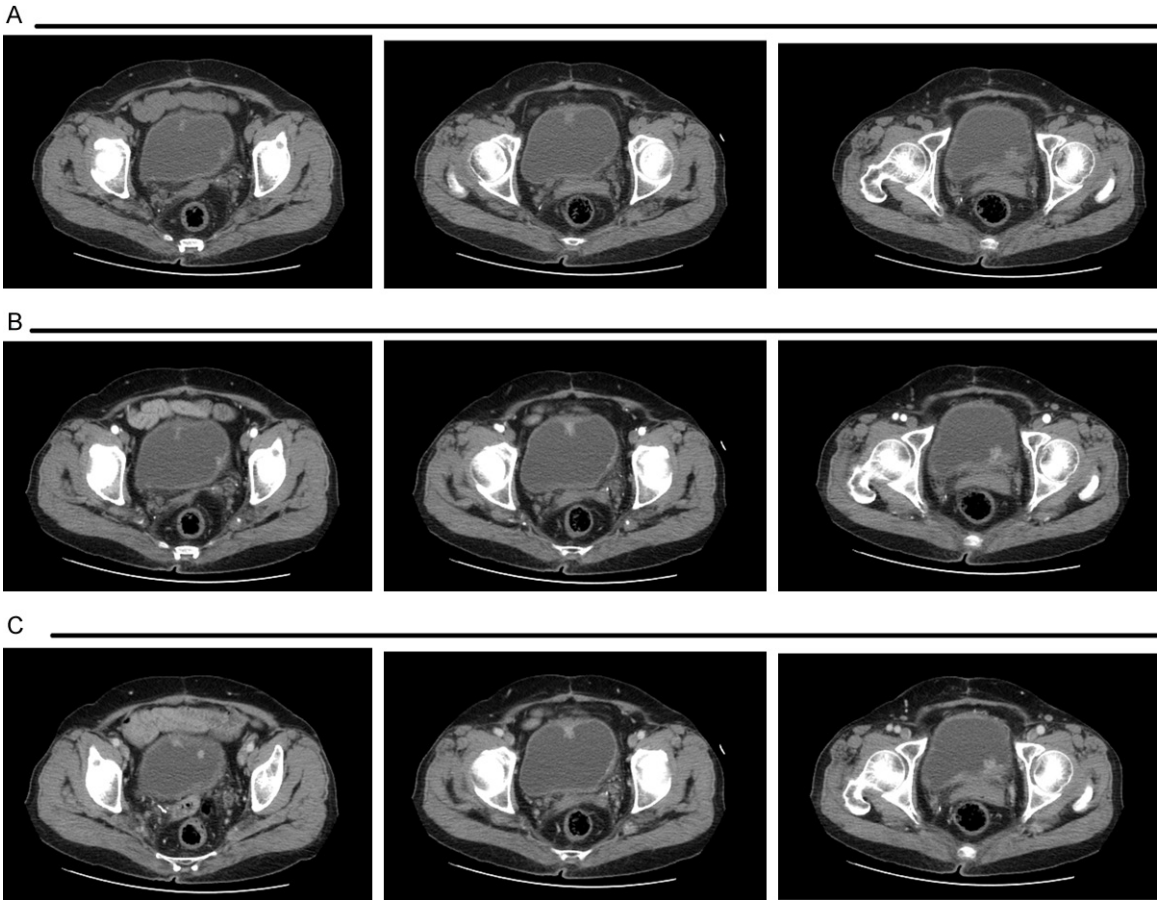

Figure 4. CT scan of urinary system showing nodular protrusion on the inner wall of the bladder. A. When the tumor volume was large (diameter ≥2 cm), the enhanced scan showed moderate enhancement; B, C. When the tumor volume was small, there was no specific performance. CT: Computed Tomography.

With a diabetes history exceeding 20 years and ongoing metformin therapy, her postprandial blood sugar consistently measured around 11.5 mmol/L. Upon admission, comprehensive examinations revealed no anomalies in blood counts, liver and kidney function, electrolytes, or lipid profiles. A CT scan of the urinary system exhibited nodular protrusions on the inner wall of the bladder (**Figure 4A**). A contrast-enhanced CT scan revealed numerous nodular elevations on the bladder wall, exhibiting moderate enhancement during the augmented phase (**Figure 4B**, **4C**). Cystoscopy unveiled a circular mass near the ureteral orifice on the left side of the bladder trigone, resembling floating seaweed within the urine. It measured about 2.5 × 1 × 1 cm with a stalk, and approximately 1 × 1 cm wide. The right ureteral orifice was unobstructed, and multiple similar masses were observable on the left and right walls and the anterior wall of the bladder (**Figure 5A**). After ruling out surgical contraindications, the patient underwent transurethral resection of the bladder tumor (TURBT). Postoperative pathology outcomes indicated bladder xanthoma, with histological analysis revealing multifocal aggregations of foam-like tissue cells (**Figure 6A**). The cells were small, possessed deeply stained cytoplasm, nuclei often skewed to one side, and exhibited abundant microcavities separating them, devoid of inflammatory or giant cells (**Figure 6B**). Immunohistochemistry findings unveiled CD68 (+), CD163 (+), Vimentin (+), CK (-), and Desmin (-) staining (**Figure 6C**). A cystoscopy follow-up after 3 months displayed the previous surgical scar but no recurrence of the tumor (**Figure 5B**).

Discussion

Xanthomas can appear in various human body tissues and are often associated with different

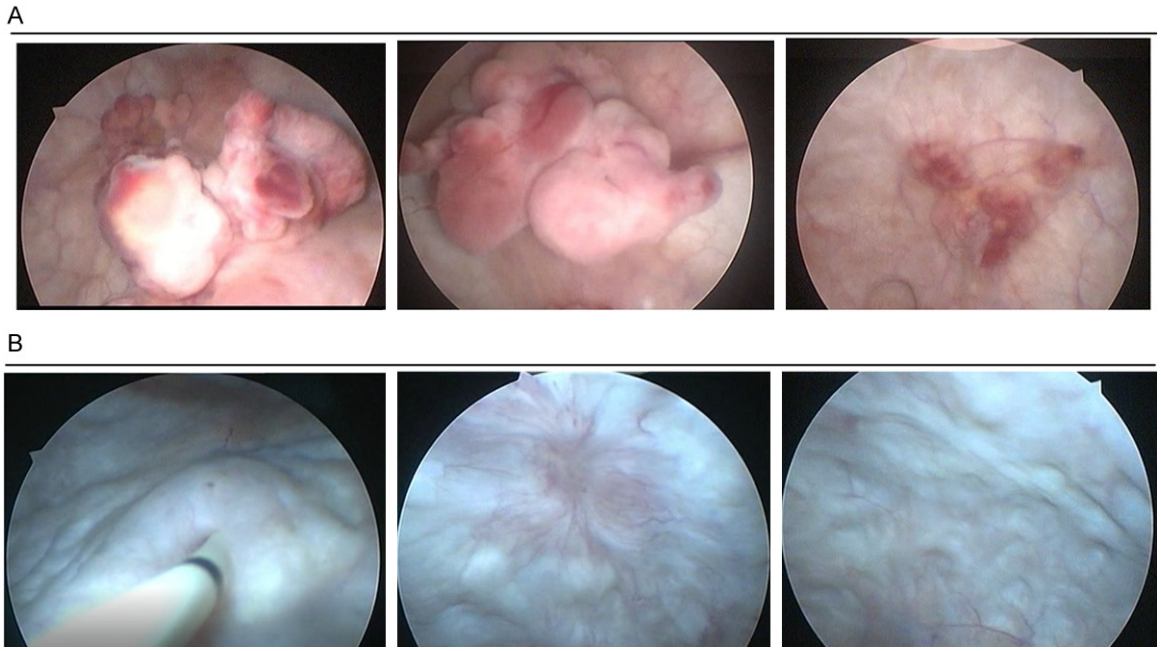

Figure 5. Cystoscopy showing coral-like masses on the walls of the bladder. A. Numerous masses on the left, right, and anterior walls, the largest at the left ureteral orifice (2.5 × 2 × 2 cm); B. Follow-up after 3 months displayed surgical scar but no tumor recurrence.

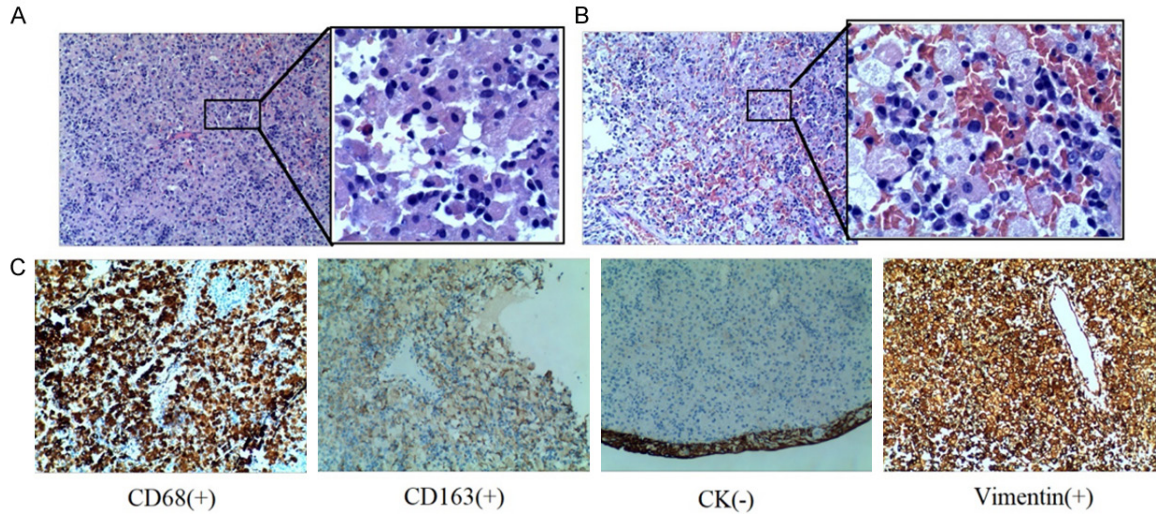

Figure 6. Histological biopsy of bladder xanthoma. (A, B) Multifocal foam cells, small in size, deeply stained in cytoplasm, often located on one side of the nucleus, with abundant microvoid separation cells. (C) Immunohistochemical results: CD68 (+), CD163 (+), vimentin (+), CK (-), desmin (-). Magnification: (A) 100 ×, 400 ×; (B) 100 ×, 400 ×; (C) 100 ×.

forms of hyperlipidemia. However, they can also develop in individuals with normal blood lipid levels. The presumed root cause is linked to familial genetic defects related to lipid and lipoprotein abnormalities. Secondary factors may include chronic conditions such as diabetes, hypothyroidism, and atherosclerosis, often accompanied by elevated levels of serum cholesterol, triglycerides, and lipoproteins. The precise pathogenesis of bladder xanthoma remains unclear. In the literature, 16 cases (50%) of patients exhibited anomalies in lipid metabolism, primarily elevated serum cholesterol levels, mirroring the mechanism observed

in xanthelasma formation. For some patients, localized disturbances in lipid metabolism due to surgery, trauma, or inflammatory stimuli in the lesion site led to the aggregation of foam cells, similar to the mechanism seen in gastrointestinal xanthomas. However, a subset of patients did not show any abnormalities in blood lipid tests [3]. Consequently, the development of bladder xanthoma might be associated with lipid metabolism irregularities. Bladder xanthomas are typically described as clusters of small yellow nodules or yellow-white patches. Nevertheless, reports by Nishimura et al. [4] and Skopelitou et al. [5] depict them as velvet-like yellow lesions with a pedicle, floating in the bladder - a description consistent with our observations during cystoscopy. The size of bladder xanthomas generally ranges from a few millimeters to several centimeters. Among the 22 reported cases, we analyzed the differences in tumor size between genders. Remarkably, bladder xanthomas in males were significantly larger than those in females. However, due to the limited sample size, a sufficient number of case reports are necessary to provide robust data support for this observation.

Since Miliauskas et al. first reported the initial case of bladder xanthoma, there has been a gradual increase in awareness and documentation of this condition. Nataniele et al. [6] synthesized and outlined previous investigative findings in 2018, which broadly align with the literature data we have gathered. Bladder xanthoma is a benign non-neoplastic lesion. However, approximately 50% of patients concurrently have urinary tract epithelial carcinoma. This mainly affects older male patients, with a preference for low-grade tumors, although instances of concurrent high-grade urinary tract epithelial carcinoma have also been noted. In 2000, Skopelitou et al. [5] chronicled the initial case of bladder xanthoma combined with high-grade transitional cell carcinoma of the urinary tract. Subsequently, Nataniele et al. [6] documented two similar cases in 2018: one featuring bladder xanthoma concomitant with high-grade urinary tract epithelial papillary carcinoma (pTa-G2/G3), and the other involving bladder xanthoma combined with minimally invasive urinary tract epithelial papillary carcinoma (pT1-G3). Consequently, after the diagnosis of bladder xanthoma, comprehensive surgical excision is typically recommended. Among the 22 cases collected in this study, routine follow-up cystoscopy assessments after surgical excision revealed no instances of recurrence or malignant progression.

The radiological features of bladder xanthoma are not well-defined. Color Doppler ultrasound of the urinary system often shows a slightly echogenic region within the bladder, presenting an irregular morphology similar to a solid mass. CT scans of the urinary system, especially for substantial tumor volumes (diameter ≥2 cm), may reveal nodular elevations on the bladder wall, with moderate enhancement during contrast-enhanced scans. However, smaller tumors may lack distinctive features. While MRI manifestations for bladder xanthoma are nonspecific, they aid in distinguishing it from non-malignant bladder masses, effectively ruling out malignancy [7].

Histopathologically, distinguishing bladder xanthoma from various conditions is crucial. Bladder softening disease displays foam cells in histological tissue, along with distinct alkaline Michaelis-Gutmann bodies. Xanthogranulomatous cystitis, a chronic nonspecific inflammatory granulomatous lesion, lacks Michaelis-Gutmann bodies and exhibits infiltration of inflammatory cells like plasma cells [8-16]. On the other hand, signet ring cell carcinoma is characterized by crescent-shaped nuclei pushed to one side of the cell, along with infiltration into adjacent tissue layers [17-21]. In contrast, the histopathological tissue of bladder xanthoma shows multifocal foam cell accumulation without infiltration by other cell types, thus distinguishing it from the mentioned diseases. Some researchers use immunohistochemical staining with CD68 antibodies to aid in the differential diagnosis. However, CD68 expression is present in both macrophages and tissue cells, with only signet ring cell carcinoma displaying CD68 negativity. Both bladder xanthoma and bladder softening disease exhibit CD68 positivity, making this method less specific [8, 22].

Various perspectives exist regarding the treatment of bladder xanthoma. Some experts suggest that addressing irregularities in lipid metabolism may be sufficient in cases of solitary bladder xanthoma accompanied by hyper-

lipidemia. Surgical excision of the lesion is recommended when severe clinical symptoms (e.g., gross hematuria, urinary irritation) are present or when the tumor grows unusually large or coexists with other bladder tumors [12, 23]. However, some researchers argue that despite being a rare benign condition, 50% of bladder xanthoma patients concurrently have bladder tumors, which could complicate the situation. Therefore, complete surgical removal is advised.

Bladder xanthoma is often associated with bladder urothelial carcinoma, posing a risk factor for the latter. Surgical excision is prudent upon diagnosing bladder xanthoma to mitigate the risk of coexisting tumors and complications. Endoscopic follow-up is necessary, and appropriate endoscopic treatment should be performed. The prognosis and recurrence of bladder xanthoma may be linked to patients exhibiting abnormal lipid metabolism, especially elevated levels of serum cholesterol, triglycerides, and lipoproteins. Therefore, patients with bladder xanthoma should actively control abnormal lipid metabolism. However, due to the lack of substantial evidence in evidence-based medicine, the efficacy of solely managing lipid metabolism irregularities remains uncertain.

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Disclosure of conflict of interest

None.

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