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Case Report

Localized amyloidosis of the prostatic urethra mimicking urothelial carcinoma

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Abstract: Amyloidosis is a disease characterized by extracellular deposition of amyloid protein fibrils in tissues. It rarely involves the urethra with just over 50 cases reported in the English language literature. We report a case of urethral amyloidosis that mimicked urothelial carcinoma clinically. The patient is a 69-year-old male who presented to the emergency department with shortness of breath. An abdominal CT scan demonstrated a right hydronephrotic kidney and a large, predominantly hyperdense lesion, presumed to be hematoma largely occupying the urinary bladder. Pan-cystoscopy revealed a 6 cm bladder mass involving the prostatic urethra displacing the right ureteral orifice, which was biopsied. Histologic examination showed numerous osteoclast-type giant cells, with areas of extensive calcification and multifocal ossification interspaced by large deposits of amorphous eosinophilic material. Amyloid deposition was confirmed by Congo red and sulfated Alcian blue stains. Light chromatography tandem mass spectrometry was performed and detected multiple types of proteins including serum amyloid P component, apolipoprotein A4, and apolipoprotein E; however, a dominant amyloid type was not identified. The patient had no history of infection or localized inflammation. Further investigations for systemic amyloidosis were all negative. Amyloidosis of the urethra is extremely rare and may either be localized, idiopathic or a manifestation of systemic amyloidosis. Physicians among various specialties, including urologists, pathologists and radiologists should be aware of this rare entity, as this lesion may be easily mistaken for malignancy further emphasizing the importance of tissue diagnosis before definitive surgery. Long-term follow-up in the absence of symptoms may not be required.

Keywords: Amyloid, amyloidosis, urethra, urethral stricture, urethral tumor

Introduction

Amyloidosis is a rare disease that can involve the genitourinary tract. Solomin first described a case of localized amyloidosis involving the urinary bladder in 1897 during an autopsy [1]. Since that time more than 200 cases have been published in the literature, the majority of which are individual case reports and a few case series [2-8]. Previously reported cases of localized amyloidosis occurred most often in the urinary bladder, followed by the ureter, urethra, and renal pelvis [6]. Cases of amyloidosis involving the prostate, seminal vesicles, and testis are extremely rare, typically resulting from secondary involvement by systemic amyloidosis [9-13]. In most instances, localized amyloidosis was an incidental finding of little consequence. Local surgical treatment was effective in organ-limited amyloidosis, although recurrences have been reported [3, 14, 15]. For this reason, continued surveillance may be necessary. Amyloidosis is classified as either primary amyloidosis usually without preceding or coexisting disease, secondary systemic amyloidosis with chronic inflammatory or infectious conditions, or amyloidosis associated with multiple myeloma [16]. Localized amyloidosis of the urethra is rare, first described in an autopsy case in 1909 by Tilp [17]. There have been more than 50 additional reported cases since then in the English literature, mostly from individual case reports (**Table 1**) [2, 18-58]. In two patients bladder involvement was also present [18, 21] and in one patient both the urethra and glans penis were involved [25]. It is also worth mentioning that several reports have been published in non-English language [17, 59-70]. These lesions can easily be confused with malignancy and therefore represent an impor-

Table 1. Localized urethral amyloidosis: cases published in English literature between 1932 - present (including our case)

Reference	No. of cases	Age/ Sex	Clinical presentation	Site(s)	Procedure	Tumor size	Diagnostic studies	Follow-up
Chwalla, 1932 [18]	1	57/M	Gross hematuria; urinary retention; history of papillary tumor at internal urethral orifice	Bladder neck; urethra	Partial cystectomy; urethral curettage	NR	Cystocopy, solid tumor of uneven surface	NR
Ullmann et al., 1964 [19]	1	62/M	Painless hematuria, nocturia, urinary frequency; history of gonorrhea and clear cell adenocarcinoma of right kidney	Proximal bulbourethra	Biopsy	NR	Cystoscopy, poorly delineated lesion	NR
Branson et al., 1969 [20]	1	47/M	Painless hematuria, urinary urgency, nocturia; no history of gonorrhea	Penile urethra	Biopsy	3 cm	Cystoscopy, hard, irregular, tumorous mass	NED at 10 mo after diagnosis
Gerami et al., 1970 [21]	1	60/M	Gross hematuria; dysuria; history of gonorrhea	Anterior bladder wall; urethra	Partial cystectomy; segmental resection	NR	Urethroscopy, near complete occlusion by a hard, tumor-like lesion	NED at 12 mo after diagnosis
Carris et al., 1976 [22]	1	63/M	Urethral discharge, some decreasing force of stream and occasional nocturia; no history of urethritis	Distal bulbous urethra	Biopsy followed by TUR	NR	Urethroscopy, semicircular, friable, ulcerated lesion	NED at 5 mo after diagnosis
Ordóñez et al., 1979 [23]	1	37/M	Bloody urethral discharge after coitus, lump at fossa navicularis	Fossa navicularis	Biopsy followed by meatotomy	1.5 cm	Urethroscopy, sessile, raised lesion	NED at 8 mo after diagnosis
Constantian et al., 1980 [24]	1	27/M	Bloody urethral discharge, dysuria, hesitancy, slowing urination and induration; history of urethritis	Distal penile urethra	Biopsy and internal urethrotomy with nitrofurazone urethral suppository	NR	Cystourethroscopy, somewhat hyperemic, with induration and narrowing	NED at 24 mo after after diagnosis
Bodner et al., 1981 [25]	1	21/M	Laterally deviated urinary stream, urethral pain on ejaculation, lump at tip of penis and second distinct area of firmness in distal shaft; history of gonococcal urethritis	Urethral meatus, anterior urethra proximal to fossa navicularis	Biopsy with local resection and urethrotomy followed by radical extirpation and plastic surgical reconstruction	2 cm and 1.5 cm	Physical examination, hard, discrete nodule, additional distinct but less well defined zone of nontender induration	NED at 36 mo
Fujihara et al., 1981 [2]	3	55/M	Inflammation of bladder and urethra	Urethra	Biopsy	NR	NR	NR
		25/M	Induration of penile shaft	Corpus cavernosum and urethra	Biopsy	NR	NR	NR
		26/M	Itching and pain on penis	Penile urethra	Biopsy	NR	NR	NR
Fujime et al., 1981 [26]	2	50/M	Penile tumor associated with bloody discharge, weak urinary stream	Anterior urethra	Biopsy with frozen section followed by local resection and urethral reconstruction	6.0 cm	Retrograde urethrogram, smooth narrowing	NED at 12 mo following surgery
		63/M	Urethal tumor and persistent pyuria; history of gastric cancer	Anterior urethra	Biopsy with local resection and urethroplasty	5.0 cm	Retrograde urethrogram, urethral narrowing	NED (unknown mo)
Vasudevan et al., 1981 [27]	1	61/M	Dysuria, dribbing of urine, frequency	Anterior urethra proximal to fossa navicularis	Biopsy and distal urethrectomy and perineal urethrostomy	4.5 cm	Retrograde urethrogram, marked urethral narrowing	NED at 10 mo following surgery
Walzer et al., 1983 [28]	1	32/M	Intermittent hematuria	Anterior urethra extending down to penoscrotal junction	Biopsy	NR	Urethrogram, panendoscopy, cystoscopy, reddened papillary eruption of mucous membrane	NED at 12 mo
Dounis et al., 1985 [29]	1	25/M	Nodule at meatus, dysuria, history of gonococcal urethritis	Urethra proximal to fossa navicularis	Biopsy, urethrotomy	0.8 cm	Physical examination, elastic, painless mass	NED at 36 mo
Kaisary, 1985 [30]	1	82/M	Poor urinary stream, hesitancy, dribbling of urine and frequency	Penile urethra 5 cm from external meatus	Open excision and end-to-end anastomaosis	2.0 cm	Intravenous urogram, urethroscopy, urethral narrowing	NED at 6 mo following surgery

Rosenbaum et al., 1987 [31]	1	63/M	Bloody urethral discharge	Anterior urethra 4 cm from external meatus	Biopsy, urethrotomy	NR	Cystourethroscopy, ragged mucosa	NED at 24 mo
Brown et al., 1988 [32]	1	50/M	Painless gross hematuria; history of urethral calculi	Posterior surface of proximal penile urethra	Biopsy	2.0 cm	Cystoscopy, papillary urethral mucosa lesion	NR
Christie et al., 1988 [33]	1	38/M	Bloody urethral discharge	Penile urethra	Biopsy	NR	Cystoscopy, irregular mucosal surface with areas of reddening	NED at 13 mo
Provet et al., 1989 [34]	1	40/M	Dysuria, intermittent bloody urethral discharge, decreased force of urinary stream	Anterior urethra, bulb to meatus	Biopsy	NR	Cystourethroscopy revealed erythematous urethral mucosa with shaggy whitish areas	Recurrence at 12 mo
Stillwell et al., 1989 [35]	5	48/M	Hematuria, yellow urethral discharge	Penile urethra	Biopsy	NR	Urethroscopy, ragged mucosa	NED at 24 mo
		62/M	Urinary frequency, urgency	Prostatic urethra	Biopsy and removal	NR	Urethroscopy, shaggy mucosa	NED at 120 mo
		35/M	Painless gross hematuria, hematospermia	Bulbous urethra	Biopsy and removal	NR	Urethroscopy, nodule	NED at 3 mo
		61/M	Painless gross hematuria, hematospermia	Penile urethra	Biopsy and removal	NR	Urethroscopy, ragged mucosa	NED at 12 mo
		75/M	Dysuria, urethral pain	Penile urethra	Biopsy and neodymium YAG laser	NR	Urethroscopy, ragged mucosa	NED at 36 mo
Miyamoto et al., 1991 [36]	1	27/M	Dysuria, poor urinary stream	Distal penile urethra	Biopsy, internal urethrotomy with topical application of dimethyl sulfoxide	NR	Physical examination, hard induration Retrograde urethrogram, urethral narrowing Urethroscopy, semicircicular, friable, ulcerated lesion	NED at 6 mo
Gepi-Attee et al., 1992 [37]	1	42/M	Urethral bleeding, hematuria	Mid-penile urethra	Biopsy	1.5 cm	Panendoscopy, soft irregular circumferential mucosa lesion	NED at 6 mo
Khan et al., 1992 [38]	1	70/M	Poor stream, scrotal lump	Urethra	Partial excision	NR	Cystoscopy, irregularly stenosed urethra	NED (unknown mo)
Williams et al., 1992 [39]	1	27/M	Dysuria, pain in the base of penis, hematuria; no history of urethritis	Posterior urethra	Biopsy	NR	Physical examination, meatal erythema Urethroscopy, extensive ulceration with polypoid lesion	NED (unknown mo)
Mani et al., 1993 [40]	1	33/M	Sudden onset dysuria, urgency, post-void dribbling and intermittent hematuria; childhood history of Legg-Calvé-Perthes disease; no history of urethritis	Proximal urethra	Biopsy with extraction of portion of occlusive tissue	5 cm	Physical examination, irregular, firm, mildly tender, nodular mass Retrograde urethroscopy, irregular constriction Cystoscopy, occluded urethral lumen by white fibrous, somewhat granular appearing material	NED at 18 mo
Tsujimura et al., 1993 [41]	1	54/M	Dysuria, painless induration of penile shaft	Penile urethra	Biopsy	1.5 cm	Retrograde urethrogram, irregular narrowing Urethroscopy, narrow segment with erythematous urethral mucosa covered with whitish plaque	NED at 24 mo
Lau et al., 1995 [42]	1	38/M	Painful erection	Penile urethra	Biopsy with fulguration	1 cm	Physical examination, area of induration Cystorurethroscopy, few tiny, superficial papillary lesions and other whitish, shaggy, papillary lesions	NED at 24 mo

Madersbacher et al., 1995 [43]	1	34/M	Weak urinary stream, recurrent gross hematuria	Penile urethra	Open biopsy with open urethrectomy with urethroplasty	10 cm	Physical examination, hard indurated area Retrograde cystourethrogram, marked narrowing of penile urethra	NED at 10 mo
Sakuma et al., 1996 [44]	1	65/M	Bloody spotting	Distal urethra	Biopsy	4 cm	Physical examination, irregular, firm, nodular nontender mass Retrograde urethrography, irregular narrowing Endoscopy, occluded urethral lumen	NR
Noone at al., 1997 [45]	1	28/M	Gross hematuria, dysuria	Penile urethra	Biopsy	NR	Cystourethroscopy, circumferential, partially occluding, friable, whitish plaques	NR
Hamidi Asl et al., 1998 [46]	1	29/M	Post micturition incontinence	Urethra	Biopsy with resection with end-to-end anastomosis	Tissue fragments, 0.6 cm in greatest dimenson	Cystourethroscopy, obstructive lesion	NED at 24 mo
Kageyama et al., 1998 [47]	1	39/F	Urethral pain and bleeding	Anterior vaginal wall; urethra	Biopsy	2 cm	Physical examination, brown elastic mass	NED at 60 mo
Biyani et al., 1999 [48]	1	89/M	Dysuria, UTI, hematuria; recurrent urothelial carcinoma	Urethra; bladder wall	Biopsy followed by TUR	NR	Cystoscopy, small nodule distal to external sphincter	NR
Répássy et al., 1999 [49]	1	31/M	Urethra swelling and pain	Urethral meatus	Urethrotomy	0.4 cm	Urethroscopy, urethral stricture External urethrotomy, thickened, compact, leathery, mosaic like mucosal membrane	NED at 6 mo
Crook et al., 2002 [50]	1	23/M	Tight foreskin on erection, frank hematuria, dysuria	Bulbous urethra	Biopsy, urethrotomy at 6 mo	NR	Urethroscopy, inflamed and soft tissue mass	NED at 24 mo after diagnosis
Ichioka et al., 2004 [51]	1	27/M	Difficulty voiding and palpable induration; no history of urethritis	Distal penile urethra	Biopsy	NR	CT, ill-defined enhanced tissue in urethra MRI, lesion exhibited low signal intensity on T1-weighted images and well-enhanced, relatively low signal intensity on T2-weighted images	NR
Cormio et al., 2009 [52]	1	30/M	Urethrorhagia during erection, painless palpable nodule; no history of urethritis	Penile urethra	Biopsy and wide surgical excision	2 cm	Penile ultrasound, isoechoic nodule Pelvic MRI, solid heterogeneous nodular mass, hypovascular in delay phase of contrast-enhanced imaging Urethroscopy, mucosal hyperemia	NED at 36 mo
Muneer et al., 2009 [53]	1	35/M	Palpable lump	Urethral meatus	Biopsy	NR	Physical examination, longitudinal thickening initially thought to be Peyronie's plaque	NR
Kawashima et al., 2011 [54]	1	56/M	Bladder outlet obstruction, gross hematuria	Penile urethra from fossa navicularis to bulbous urethra	Biopsy	NR	NR	NR

Mangera et al., 2012 [55]	4	50/M	Poor flow	Urethra	Biopsy with frozen section followed by augmentation urethroplasty	NR	NR	NED at 18 mo
		71/M	Poor flow, UTIs	Urethra	Biopsy with urethrostomy	NR	NR	NED at 3 mo
		38/M	Swelling penile shaft, poor flow, UTIs, history of chlamydial urethritis	Urethra	Biopsy with frozen section followed by augmentation urethroplasty and urethrostomy diversion, followed by further resection	NR	NR	NR, awaiting urethrostomy reversal
		42/M	Pain and spraying during voiding, painful erections	Urethra	Biopsy, refused treatment	NR	NR	NR, under surveillance, AL amyloid identified by IHC
Kurbatov et al., 2015 [56]	1	34/M	Weak stream, urinary frequency, painful urination; history of gonococcal urethritis	Penile urethra	Biopsy with augmentation urethroplasty	NR	Retrograde urethrogram, continuous urethral narrowing	NED at 24 mo
Yao et al., 2017 [57]	2	39/M	Recurrent hematuria and bloody secretions	Penile urethra	Biopsy with augmentation urethroplasty	4 cm	Urethroscopy, localized lesion and extensive circular ulcerations and polypoid changes	NED at 24 mo
		59/M	Recurrent hematuria and bloody secretions	Penile urethra	Biopsy with augmentation urethroplasty	7 cm	Urethroscopy, localized lesion and extensive circular ulcerations and polypoid changes	NED at 36 mo
Isaacson et al., 2020 [58]	1	33/M	Urinary frequency and difficulty voiding; no history of STI	Penile urethra, mid-penile shaft to the distal aspect of the membranous urethra	Biopsy with local resection and urethroplasty	8 cm	Retrograde urethrogram, bulbar stricture Anterior urethroplasty, irregular, firm, nodular mucosa	NED (unknown mo)
Current case	1	69/M	Presented to ED with SOB, evaluated by CT showing right hydronephrosis with question of bladder tumor	Prostatic urethra with obstructed right ureteral orifice	TUR	5-6 cm	Cystoscopy, infiltrative and obstructing urethral mass	NED at 4 mo, amyloid subtype, indeterminate by LC MS/MS

CT, computed tomography; ED, emergency department; IHC, immunohistochemistry; LC MS/MS, liquid chromography tandem mass spectrometry; MRI, magnetic resonance imaging; NED, no evidence of disease; NR, not reported; SOB, shortness of breath; STI, sexually transmitted infection; TUR, transurethral resection; UTI, urinary tract infection.

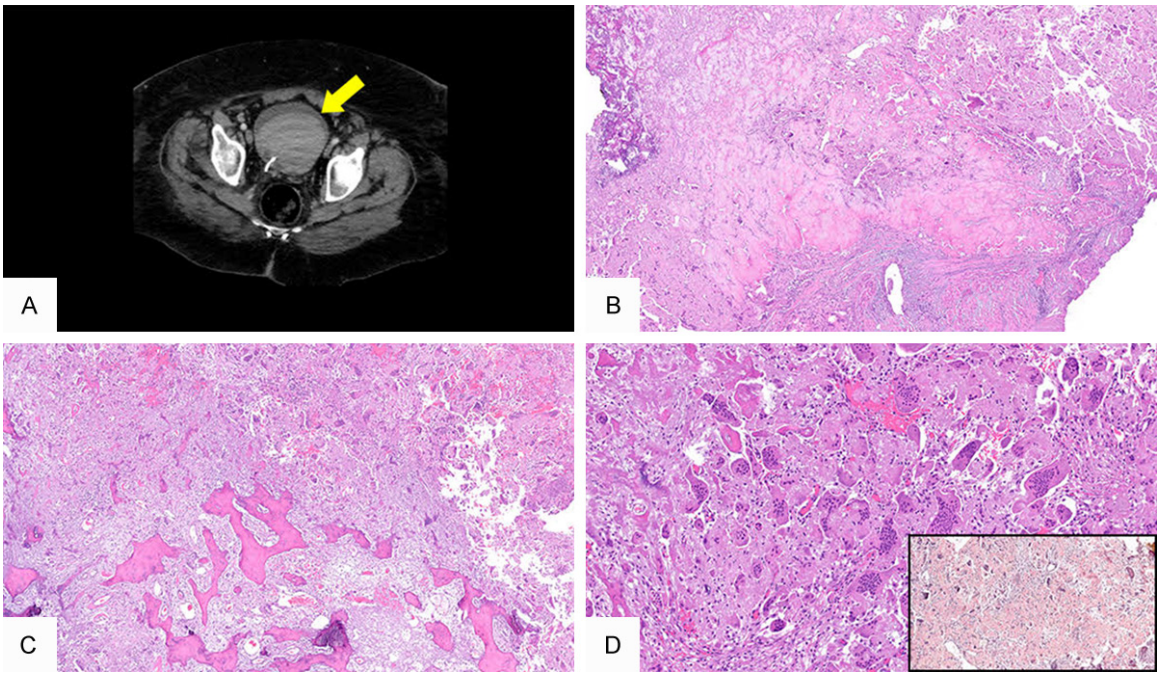

Figure 1. CT imaging and histological examination. A. Abdominal CT scan showing right hydronephrotic kidney and urinary bladder largely occupied by a large, predominantly hyperdense lesion, presumed hematoma. B-D. Urethral mass with large deposits of amorphous eosinophilic material associated with numerous osteoclast-type giant cells, with areas of calcifications and multifocal ossification. D inset. Amyloid deposits confirmed by Congo red stain.

tant differential diagnostic pitfall. Patients frequently present with non-specific symptoms, therefore histologic examination is essential for diagnosis. We report a case of localized urethral amyloidosis that was clinically suspected to be urothelial carcinoma involving the urethra. Our goal is to briefly review the spectrum of disease presentations of localized amyloidosis and evaluate management of the disease.

Case presentation

A 69-year-old male presented with gross hematuria. He had no history of gonorrhea, chronic systemic or localized inflammatory disease, or related symptoms. Significant laboratory data included urinalysis positive for red blood cells, negative urine culture, negative gonococcal and chlamydial cultures, negative serum and urine electrophoresis, and normal erythrocyte sedimentation rate. Contrast tomography (CT) scan detected a hydronephrotic right kidney with question of a bladder tumor (**Figure 1A**). Cystourethroscopy showed a 6 cm infiltrating mass within the prostatic urethra. The majority of the mass was resected but could not be removed entirely by transurethral resection. Histologic sections revealed large deposits of eosinophilic material present within the submucosa with areas showing calcification and multifocal ossification (**Figure 1B-D**). This eosinophilic material was amorphous in appearance and was associated with numerous osteoclast-type giant cells. Between the deposits of this material and at the periphery were spindle cells, which showed minimal nuclear atypia and hyperchromasia. Spindle cells associated with foci of ossification show immunopositivity for SATB2, while negative for CAM5.2 and pancytokeratin. Amyloid deposits were confirmed by Congo red (**Figure 1D** inset) and sulfated Alcian blue stains. Light chromatography tandem mass spectrometry was performed on peptides extracted from Congo red-positive amyloid deposits and detected multiple types including serum amyloid P component, apolipoprotein A4, and apolipoprotein E; however, a dominant amyloid type was not identified. The patient was subsequently referred to an oncologist for further investigations to exclude systemic disease and requirement for further treatment. Quantitative serum immunoglobulin tests were within normal range (immunoglobulin A, 1.93 g/dL, range 0.8-4.0 g/dL; immu-

noglobulin G, 9.35 g/dL, range 6.0-16.0 g/dL); immunoglobulin M, 1.3 g/dL, range 0.5-2.0 g/dL). A serum protein electrophoresis demonstrated decreased albumin (2.97 g/dL, range 3.8-5.0 g/dL) and slightly elevated alpha-2 globulin (1.21 g/dL, range 0.6-1.0 g/dL) with a normal kappa-lambda free light chain ratio (1.37) and serum protein immunofixation electrophoresis. Four months following the initial diagnosis the patient remains free of symptoms and under surveillance.

Discussion

Amyloidosis can either be localized to one organ such as skin, lung, urinary or gastrointestinal tract, or systemic affecting multiple organ systems. Localized disease is often caused by local production of immunoglobulin light chains and typically appears as one tumor-like lesion, although multiple lesions may occur. These usually do not progress to systemic amyloidosis [71]. The most frequently encountered types of systemic forms are light chain (or primary AL amyloidosis), inflammation-related (or secondary AA amyloidosis), transthyretin (or ATTR amyloidosis), and β_2-microglobulin (or Aβ_2M amyloidosis commonly associated with renal dysfunction and long-term dialysis). These may either be inherited or acquired and tend to show specific organ predilection [72, 73]. The cause of primary amyloidosis of the urethra is unknown. Secondary forms may occur in association with chronic inflammatory disorders such as rheumatoid arthritis, tuberculosis, or pre-existing gonoccocal infection [24, 25].

Our patient presented at age 69, slightly older than the mean age of patients previously reported in the English language literature, which is 46 years (range 21 to 89 years). All reported cases were confined to males, except for one case occurring in a female [47]. Patients most commonly present with symptoms of hematuria, dysuria, or urethral obstruction. As in our case, irregular urethral narrowing may result in hydronephrosis mimicking urothelial carcinoma. A history of infectious urethritis, with *Neisseria gonorrhea* and *Chlamydia trachomatis* being the most common causative organisms, were noted in several cases [19, 21, 24, 25, 29, 55, 56]. The lesion in our case was larger than the mean lesion size previously reported (6 cm vs 3.4 cm). The largest lesion size reported thus far is 10 cm [43]. The diagnosis was made in all reported cases following biopsy of the lesions. As part of the evaluation, it is important to pursue further workup to exclude systemic disease. Congo red stain is the gold standard for the demonstration of amyloid in tissue sections. Amyloid protein typing is useful in determining the origin of amyloid deposition and may be warranted to identify the underlying disease process.

Many treatment modalities for localized disease have been utilized and are based on symptom severity. In reported cases patients have been treated surgically in order of decreasing frequency, with internal urethrotomy, 7 [29, 31, 49, 50], 1 with nitrofurazone urethral suppository [24] and 1 with topical dimethyl sulfoxide [36]; resection and end-to-end anastomosis, 3 [21, 30, 46]; local resection and urethroplasty, 3 [26, 58]; urethrectomy with urethrostomy, 2 [27, 43]; transurethral resection, 2 [22, 48]; cup biopsy with fulguration, 1 [42]; meatotomy, 1 [23]; urethrostomy, 1 [55]; or urethral curettage, 1 [18]. In one case progression of disease required radical extirpation and plastic surgical reconstruction following local resection with urethrotomy [25]. In severe penile involvement,augmentationurethroplastywasperformed, 5 [55-57].

The majority of cases had an indolent clinical course, however to date two cases with recurrence have been reported [19, 44]. Progression to systemic amyloidosis has not been reported. Overall our patient had an outcome similar to those of previous reports.

Conclusion

Primary localized urethral amyloidosis should be considered a rare differential diagnosis in patients with urethral stricture, due to the similarities in clinical presentation with urothelial malignancy and represents a diagnostic and management challenge. A biopsy should be performed to confirm diagnosis, followed by investigations for systemic involvement. This disease rarely recurs and is usually not associated with multiple myeloma or systemic forms of the disease. Localized urethral amyloidosis may be managed by observation or local resection.

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We confirm all relevant ethical guidelines have been followed. We consulted with the Institutional Review Board/Research Ethic Committee of Indiana University who determined that ethical approval was not applicable because this article does not contain any studies with human or animal subjects. Written informed patient consent was obtained and the appropriate institutional forms have been archived for this publication.

Disclosure of conflict of interest

None.

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