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Original contribution

Amyloidosis of the bladder and association with urothelial carcinoma: report of 29 cases☆,☆☆

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Summary The association of amyloidosis with certain neoplastic processes is well known. Amyloid uncommonly occurs in relationship with other epithelial neoplasms including urothelial carcinoma. Herein, we report 29 cases of amyloidosis in the bladder, 14 of which were found in relationship to urothelial carcinoma. With institutional review board approval. We searched pathology archives for cases of amyloidosis in the bladder. Clinical, laboratory, and surgical pathology records were reviewed, and data were recorded for all cases. Diagnosis of amyloid was made by Congo red stain showing apple-green birefringence on polarization microscopy and special studies in some cases. Twenty-nine cases of amyloid were identified in bladder specimens. Presentation as a mass lesion was the most common (n = 18). Immunohistochemical subtyping done in 17 cases showed transthyretin-type (n = 10), AL (n = 3), AA (n = 1), amyloid P (n = 1), and undetermined (n = 2) types of amyloid. Eighteen (62%) cases were classified as localized primary amyloidosis and 11 (38%) as secondary manifestation of systemic amyloidosis. In 14 (48%) cases, there was an associated urothelial carcinoma: 5 urothelial carcinoma in situ, 4 low-grade noninvasive papillary urothelial carcinoma, 2 high-grade noninvasive papillary urothelial carcinoma, and 3 high-grade invasive urothelial carcinoma. Associated urothelial carcinoma was present in 4 of 7 patients with systemic amyloidosis and 10 of 18 patients with localized amyloidosis, with the difference not being statistically significant (P = .45). Amyloidosis of the bladder is rare and presents as a mucosal mass or hematuria that may mimic urothelial carcinoma. In this study, we found urothelial carcinoma occurring in 48% of the cases in association with amyloidosis, a finding not previously reported. The relationship of amyloid in the bladder and urothelial carcinoma, although likely not causal, appears to be a unique finding not frequently seen with other solid tumors.

1. Background

Amyloidosis is a rare group of disorders due to deposition of fibrillary matrix material derived from precursor amyloidogenic proteins in extracellular space occurring in diverse inherited, inflammatory, or neoplastic conditions. Detection of amyloid in surgical pathology practice is not uncommon

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and may provide important diagnostic clues in challenging cases. In many instances, it is an incidental or even an unexpected pathologic finding in a clinically suspicious mass lesion that may mimic a neoplasm. The association of amyloid is well known in hematologic and endocrine malignancies but is rarely seen in association with other solid tumors. In recent years, some studies have demonstrated the role of amyloid precursor protein (APP) in oncogenesis in several cancers [1-5]. Upregulation of APP has more recently been shown in bladder cancer compared to matched normal tissue [6], with higher expression seen to correlate with tumor size, grade, stage, and male sex. The study further demonstrated the role of APP in promoting proliferation, migration, invasion, and cell cycle progression of bladder cancer cells mediated through regulation of the ERK signaling pathway.

Localized forms of amyloidosis have been described in the genitourinary tract mostly as case reports and small series, with the largest series of 31 patients of primary localized amyloidosis of the bladder [7,8]. Of these, there have been only 3 previous case reports of primary localized amyloidosis of the bladder occurring in association with urothelial carcinoma [9-11]. In our practice, we were intrigued by a few cases of bladder amyloidosis with some also showing concomitant urothelial carcinoma. These observations paved the way for this retrospective study with an objective to evaluate the etiopathology of bladder amyloidosis and ascertain its relationship, if any, to bladder carcinoma.

2. Materials and methods

A retrospective search of the electronic database of previously reported cases was performed for amyloidosis in bladder tissue spanning 13 years from 2005 to 2019 of the departmental and the consult files of 1 author (M. B. A.). Reports and available slides were retrieved for all cases. Hematoxylin and eosin–stained slides, special studies including Congo red stain, and immunohistochemical (IHC) stains were reviewed for confirmation, morphological distribution, associated pathologies, and subtyping of amyloid. Clinical records were reviewed for evidence of systemic amyloidosis, hematologic malignancies, chronic inflammatory disorders, or significant family history and follow-up. Laboratory results including serum protein electrophoresis and, where available, mass spectrometry (MS) data for amyloid subtyping were recorded. Data analysis was performed by Fisher exact test and χ^2 test. Statistical significance was defined by $P < .05$.

3. Results

We identified 29 cases of bladder amyloidosis in bladder specimens (Table). The specimens included 18 biopsies, 9 transurethral resections, and 2 cystoprostatectomies. The patients' age ranged from 48 to 102 years (mean 75.4; median 77) with a male predominance (male to female ratio of 4.8:1). The clinical presentation included mass lesions (n = 18) (Figure A), hematuria (n = 7), benign prostatic hyperplasia (n = 1), urinary tract infection (n = 1), and unspecified (n = 2). The amyloid deposits were seen in the stroma, in diffuse, nodular, or perivascular distributions (Figure B-E). Diagnosis of amyloidosis was confirmed by Congo red stain showing apple-green birefringence on polarization microscopy (Figure F and G). Subtyping of amyloid was done in 17 cases by IHC studies, and in 4 cases, MS was also performed. Immunohistochemical typing of amyloid included transthyretin type (n = 10) (Figure H), AL (n = 3), amyloid P (n = 1), and undetermined (n = 2). In 1 case where amyloid was not typed on the bladder specimen, there was evidence of AA amyloid on a renal biopsy by immunohistochemistry. MS was done in 4 cases (including 2 cases with IHC) on peptides extracted from Congo red–positive microdissected areas of paraffin-embedded tissue. The peptide profile in 2 cases confirmed the IHC findings of transthyretin-type amyloid and, in 1 case, was consistent with immunoglobulin-associated amyloid deposition (AL type). The fourth case had AL-type amyloid deposits in the bladder besides also having transthyretin-type amyloid deposits in heart. Serum protein electrophoresis done in 7 cases was negative in 5 and identified AL bands in 2 cases that also had AL-type amyloid in bladder.

Based on the amyloid subtyping and deposition in 1 or more than 1 organ, 18 cases were classified as localized amyloidosis and 11 as manifestation of systemic amyloidosis (involvement of more than 1 organ). Cases with systemic amyloidosis had evidence of cardiac amyloidosis (n = 6), renal amyloidosis (n = 1), lung (n = 1), and advanced amyloidosis with hepatic and cardiac involvement (n = 1). In 1 case, amyloid was subtyped as amyloid P and hence was considered to be systemic rather than localized, and 1 case of amyloid was secondary to myeloma and considered systemic. Associated urothelial carcinoma was present in 14 (48%) cases. These were classified as follow: 5 urothelial carcinoma in situ, 4 low-grade noninvasive papillary urothelial carcinoma, 2 high-grade noninvasive papillary urothelial carcinoma, and 3 high-grade urothelial carcinoma invasive into the lamina propria and muscularis propria. Associated urothelial carcinoma was present in 4 of 11 patients with systemic amyloidosis and 10 of 18 patients with localized amyloidosis, with the difference not being statistically significant ($P = .45$). Cases with urothelial carcinomas included transthyretin-type (n = 6) and AL-type (n = 1) amyloid. Amyloid subtypes did not show a statistically significant difference with presence of carcinoma ($P = .22$).

In urothelial carcinoma cases, amyloid deposits were seen in the stroma immediately beneath or adjacent to the tumor, but never as an integral part of the tumor. In the 7 cases with urothelial carcinoma in which subtyping of amyloid was performed, the amyloid subtype was transthyretin in 6 and AL in 1. Follow-up information was available in 19 cases over a

Table Clinical, morphological and laboratory features of cases of bladder amyloidosis.

	Age	Sex	Clinical presentation	Surgical procedure	Associated histology	Amyloid type	Follow-up (mo)	SPEP	Systemic/localized
1	79	M	Tumor	TUR	Normal mucosa	AA, on renal bx	–	Negative	Systemic (renal)
2	70	M	–	Biopsy	Normal mucosa	Amyloid P+	6, NED	Negative	Systemic (Amyloid P)
3	82	F	Hematuria	Biopsy	Normal mucosa	AL-kappa	–	–	Systemic (cardiac, hepatic)
4	83	F	Hematuria, 2- cm mass	Biopsy	Normal mucosa	Undetermined	16, died (cardiac)	–	Systemic (cardiac)
5	69	F	UTI	Biopsy	Normal mucosa	AL	–	AL	Systemic (lung)
6	71	M	Hematuria	Biopsy	Normal mucosa	TTR-S (IHC and MS)	12, died (cardiac)	–	Systemic (cardiac)
7	66	M	Hematuria	TUR	Normal mucosa	AL, bladder (MS) TTR-S, heart (MS)	24, NED	–	Systemic (cardiac)
8	79	M	Tumor	TUR	LGPUC, noninvasive	–	3, NED	–	Systemic (cardiac)
9	88	M	Hematuria	TUR	LGPUC, noninvasive, UCIS	TTR-S	6, NED	–	Systemic (cardiac)
10	90	M	Hematuria, tumor mass recurrence	TUR	HGPUC, noninvasive	TTR-S (IHC and MS)	24, carcinoma	–	Systemic (cardiac)
11	67	M	Hematuria	TUR	UCIS	AL	24, NED	AL	Systemic (AL secondary to myeloma)
12	62	F	Lesion	Biopsy	Normal mucosa	Ig-associated amyloid (MS)	5, NED	Negative	Localized
13	97	F	Lesion	Biopsy	Normal mucosa	TTR-S	17, carcinoma	–	Localized
14	50	M	–	Biopsy	Normal mucosa	Undetermined	–	–	Localized
15	71	M	Incidental mucosal nodules	Biopsy	Normal mucosa	TTR-S	3, NED	–	Localized
16	76	M	Hematuria, lesion	Biopsy	Urothelial hyperplasia, focal	TTR-S	108, NED	–	Localized
17	48	M	Hematuria, hyperemic patch	Biopsy	Urothelial hyperplasia with cytologic atypia	–	–	–	Localized
18	55	M	Tumor	Biopsy	Mild reactive atypia	–	–	–	Localized
19	89	M	Tumor	TUR	LGPUC, noninvasive	TTR-S	20, NED	Negative	Localized
20	86	M	Tumor	Biopsy	LGPUC, noninvasive	TTR-S	34, NED	–	Localized
21	88	M	Bladder cancer	Biopsy	LGPUC, noninvasive	TTR-S	14, died (cardiac)	–	Localized
22	102	M	Tumor	TUR	HGPUC, noninvasive	–	19, AWD	–	Localized
23	56	M	Tumor	Biopsy	HGUC, noninvasive	–	–	–	Localized
24	91	M	BPH with LUTS	Biopsy	UCIS	–	–	–	Localized
25	81	M	Mass	TUR	UCIS	–	13, carcinoma	–	Localized
26	62	M	Tumor	Cystoprostatectomy	HGPUC, invasive LP	–	56, NED	–	Localized
27	77	M	Mass	Biopsy	HGUC, invasive LP	–	–	–	Localized
28	83	M	Urothelial carcinoma	Cystoprostatectomy	HGPUC, invasive MP	TTR-S	32, NED	Negative	Localized
29	69	M	Hematuria, stones, nephrogenic metaplasia	Biopsy	Nephrogenic adenoma	–	–	–	Localized

Abbreviations: AA, amyloid A; AL, amyloid light chain; AWD, alive with disease; Ca, carcinoma; BPH, benign prostatic hyperplasia; HGPUC, high-grade papillary urothelial carcinoma; HGUC, high-grade urothelial carcinoma; Ig, Immunoglobulin; LGPUC, low-grade papillary urothelial carcinoma; LP, lamina propria; LUTS, lower urinary tract symptoms; MP, muscularis propria; NED, no evidence of disease; SPEP, serum protein electrophoresis; TTR-S, transthyretin-senile; TUR, transurethral resection; UC, urothelial carcinoma; UCIS, urothelial carcinoma in situ; UTI, urinary tract infection.

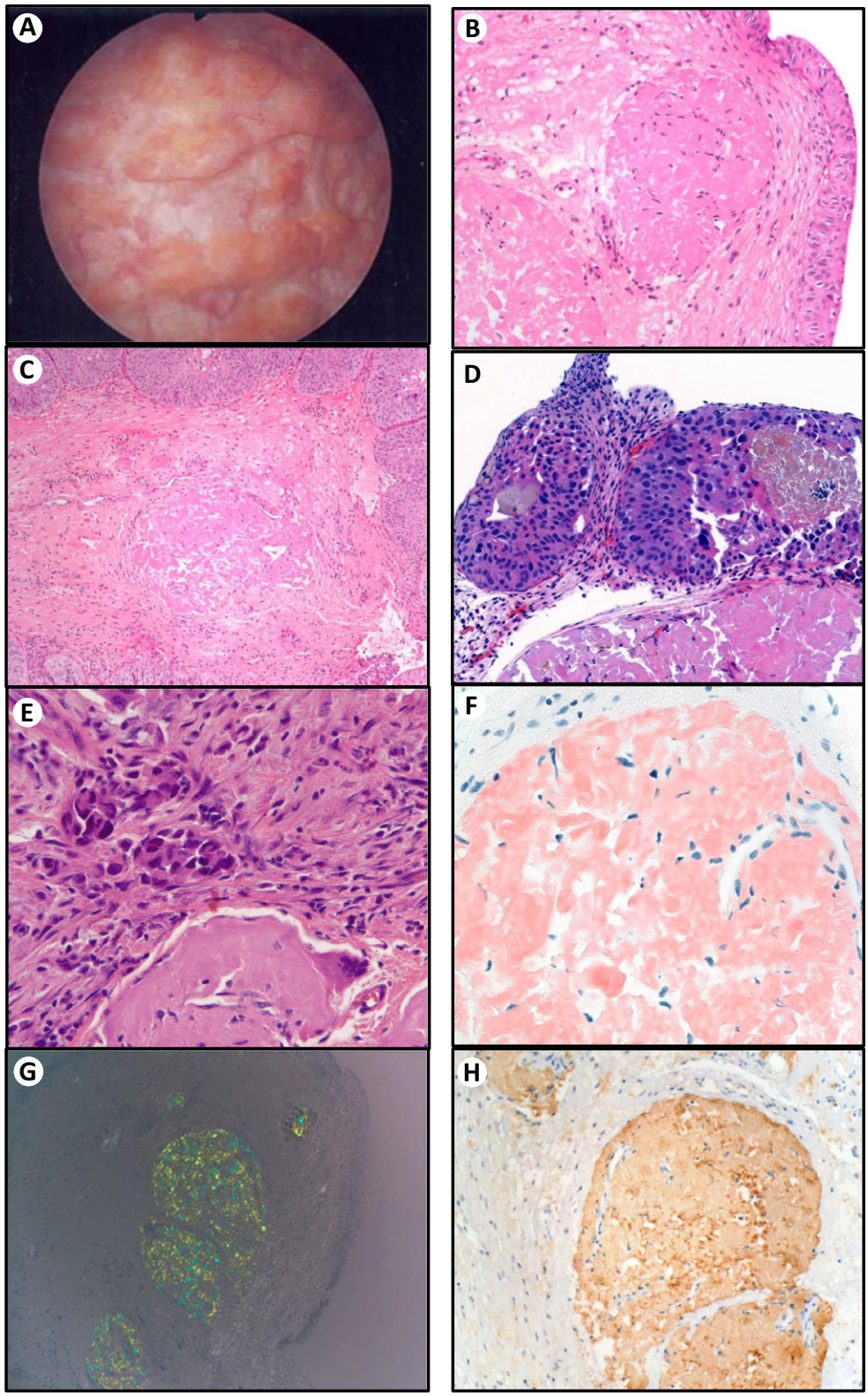

Figure A, Cystoscopy: bladder amyloidosis seen as diffuse and nodular submucosal deposits. B, Homogenous eosinophilic amyloid deposits seen in the lamina propria underneath benign urothelium (original magnification ×100). C, Amyloid deposits seen in lamina propria underlying papillary urothelial carcinoma (×40). D, Amyloid deposits seen in association with overlying urothelial carcinoma in situ (×200). E, Amyloid deposits seen adjacent to invasive urothelial carcinoma (×400). F, Diffuse strong orangeophilic staining of amyloid deposits on Congo red stain (×400). G, Apple-green birefringence of amyloid deposits stained with Congo red on polarization (×20). H, Strong diffuse positivity of amyloid deposits for transthyretin on immunostaining (×200).

period ranging from 3 to 108 months (mean 23; median 17). Three cases with systemic amyloidosis with cardiac involvement died after 12-16 months of diagnosis because of cardiac failure. Of the other 16 cases, 12 had no evidence of disease (7 with associated urothelial carcinoma), 1 was alive with disease (had associated urothelial carcinoma), 1 developed urothelial carcinoma on follow-up biopsies, and 2 had recurrence of carcinoma (both with associated urothelial carcinoma).

4. Discussion

Amyloidosis is a group of disorders characterized by progressive tissue destruction due to deposition of extracellular fibrillary matrix. From a clinical perspective, amyloidosis is classified as primary when it is associated with plasma cell dyscrasias and hematologic malignancies resulting in AL amyloidosis. Secondary amyloidosis occurs in a setting of chronic inflammatory disorders resulting in AA amyloidosis derived from serum amyloid A. Both primary and secondary amyloidosis may occur in a systemic form with involvement of multiple organs or be localized to a single organ. Localized amyloidosis is usually of the AA type but rarely can also be of the AL type. Common sites of localized deposits of amyloid include the lung [12], larynx [13], skin [14], gastrointestinal system [15], breast [16], tongue [17], and periorbital region [18]. Localized deposits may be clinically concerning because of presentation as mass lesions or organ-specific symptoms like hematuria that may suggest a neoplastic process. Certain types of amyloidosis like cerebral amyloidosis and amyloidosis associated with endocrine tumors almost always occur in a localized form, whereas other forms can occur in either a localized or systemic form and therefore require staging for accurate classification [19]. Biopsy of abdominal fat is usually recommended for purpose of amyloid staging. Localized forms clinically differ from systemic forms because these may require follow-up because of likelihood of progression to systemic form. They also need to be differentiated from systemic amyloidosis because of the different therapeutic approaches including systemic chemotherapy and even liver transplantation for systemic forms.

The association of amyloidosis with solid organ neoplasms is rare other than for hematolymphoid and endocrine neoplasms. There have been anecdotal reports of amyloidosis occurring in association with carcinomas of the breast [20-22], uterus [23], cervix [24,25], stomach [26], nasopharynx [27,28], larynx [29], lung [30], renal pelvis [31], ureter [32,33], and bladder [9-11].

There have been 3 prior reports of bladder amyloidosis occurring in association with urothelial carcinoma [9-11]. In another series, 2 cases of amyloidosis were detected on follow-up for urothelial carcinoma [34]. In individual case reports, amyloidosis has been reported in association with urothelial carcinoma of the ureter and upper urothelial tract [31-33].

In our study, the mean age of the patients was 75.4 years (range, 50-102), which is similar to previous reports [7,8,34,35] of 55, 72, 73, and 57.5 years. Like earlier studies, amyloidosis was more common in men (male/female 4.8:1). Clinical presentation as a mass lesion in 62% was the commonest presentation, as compared to hematuria being the commonest presentation in prior studies. Hematuria alone was the presenting symptom in 17% (n = 5) and hematuria with hyperemia and stones in 7% (n = 2) of cases. Benign prostatic hyperplasia and urinary tract infection were the presenting symptoms in 3% (n = 1) of cases each, whereas 7% (n = 2) of cases were diagnosed incidentally during workup for bladder carcinoma. Of the 17 cases in which amyloid typing was performed, transthyretin was the most common subtype (59%), in contrast to previous studies that report AL as the commonest subtype. Urothelial carcinoma was present in 48% of the cases. Interestingly, in the 7 cases of urothelial carcinoma in which amyloid subtyping was done, it proved to be transthyretin type in 86% (n = 6) and AL in 14% (n = 1).

Our study has several limitations. This is a retrospective study with limited follow-up on all cases. A complete amyloid staging was not performed on all cases, and the classification into systemic and localized was done based on the available clinical information of involvement of other organs and the subtyping of amyloid. The amyloid subtyping was done by immunohistochemical stains in almost all cases that has its own interpretative challenges [19], limiting the accurate classification.

The pathogenesis of localized amyloid deposits in the bladder is uncertain. The absence of a monoclonal plasma component reasons a local production of amyloid in the bladder, but the lack of an inflammatory lymphoplasmacytic component in some cases suggests alternate mechanism [34]. Another hypothesis that seems likely is that the bladder by virtue of its role of eliminating toxins is exposed to environmental toxins over a long time. This in turn could evoke an inflammatory response and result in amyloid deposits as also seen in many other chronic inflammatory conditions. The localized amyloid deposits seen in other organs lacking a definitive causative association also are for the most part in organs directly exposed to environmental toxins including potentially known carcinogens. The coexistence of amyloid with bladder carcinoma would then seem reasonable, with both occurring consequent to environmental toxins without a direct causative association.

5. Conclusions

Amyloidosis of the bladder is a rare condition and can be the manifestation of localized deposits or systemic disease. It presents as a mucosal mass or hematuria that can clinically mimic urothelial carcinoma. In this study, 48% of cases of bladder amyloidosis were associated with urothelial carcinoma. Amyloid deposits were present in the stroma adjacent

to urothelial carcinoma but not an integral part of the tumor. The relationship of amyloid in the bladder and urothelial carcinoma, although likely not causal, appears to be a unique finding not frequently seen with other solid tumors.

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