Original Article
Primary localized amyloidosis of the urinary tract frequently mimics neoplasia: a clinicopathologic analysis of 11 cases

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Abstract: Localized urinary tract amyloidosis (UTA) is a rare disease that mimics neoplasia clinically, cystoscopically, and radiologically. We report eleven cases of isolated UTA from the urinary bladder (n=7) and upper urinary tract including the ureter (n=2) and renal pelvis (n=2). All cases clinically presented as mass lesions prior to histologic examination and clinically suggested a neoplastic process. The amyloid composition in most cases was mixed Kappa and Lambda light chains. All cases were cured after surgical excision except one case which was diagnosed as plasmacytosis/plasmacytoma six months later. Localized amyloidosis of the urinary tract usually has a benign clinical course and simple resection is recommended after systemic disease is ruled out.

Keywords: Urinary tract amyloidosis, mimicker, neoplasia

Introduction

Amyloidosis is a heterogeneous group of disorders associated with mainly extracellular deposition of insoluble eosinophilic fibrillar protein in a beta-pleated configuration. It can be primary, secondary or hereditary and the deposits can be systemic or localized [1]. Localized amyloidosis (also called “amyloidoma”) is currently divided into two groups: Immunoglobin light chain amyloidosis (AL-type) and “senile” localized amyloidosis [2]. Localized amyloidosis is rare but can be seen in many sites including lung, trachea, larynx, tongue, skin, nervous system, gastrointestinal system, and urinary tract.

Within the genitourinary system, the prostate and seminal vesicles are most commonly involved by localized amyloidosis and are usually asymptomatic incidental findings in prostate specimens [3]. Localized urinary tract amyloidosis (UTA) other than prostate and seminal vesicles is very rare and is of interest to physicians of various specialties, including radiologists, urologists and pathologists, because it mimics urothelial cell carcinoma clinically, cystoscopically, and radiologically [4]. Here we report 11 cases of isolated UTA in the bladder, ureter and renal pelvis and review their clinicopathologic characteristics, emphasizing their benign clinical course and the need for conservative management.

Materials and methods

We conducted a retrospective systematic search for UTA in our electronic surgical pathology database (January 1993 to December 2013) at our tertiary care medical center, using the keyword “amyloid” combined in turn with the keywords “ureter”, “pelvis”, “bladder”, and “urethra”. Electronic medical records were reviewed for information regarding demographics, clinical history, radiologic or cystoscopic findings, histopathologic findings, amyloid immunohistochemical characterization, clinical management, and follow-up information. Ten cases had evidence of workup to exclude systemic amyloidosis. Mortality status was determined based on the Social Security Death Index (SSDI). Patients with primary systemic amyloidosis and amyloidosis secondary to rheumatic conditions, infections and malignancies at the time of diagnosis were excluded.
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Table 1. Clinical Characteristics and Pathological Findings

<table>
<thead>
<tr>
<th>#</th>
<th>Sex &amp; Age</th>
<th>Site</th>
<th>Amyloid Type(s)</th>
<th>Symptoms</th>
<th>Treatment</th>
<th>Follow-up time (months)</th>
<th>Systemic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F 74</td>
<td>Bladder</td>
<td>LC (κ&gt;λ)</td>
<td>Hematuria, mass</td>
<td>TUR</td>
<td>64</td>
<td>Yes</td>
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<tr>
<td>2</td>
<td>F 64</td>
<td>Bladder</td>
<td>n/a</td>
<td>Hematuria, mass</td>
<td>TUR</td>
<td>116</td>
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<tr>
<td>3</td>
<td>M 82</td>
<td>Bladder</td>
<td>n/a</td>
<td>Hematuria</td>
<td>TUR</td>
<td>30</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>M 89</td>
<td>Bladder</td>
<td>n/a</td>
<td>Irritation, mass</td>
<td>TUR</td>
<td>37</td>
<td>No</td>
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<tr>
<td>5</td>
<td>F 58</td>
<td>Bladder</td>
<td>LC (λ&gt;κ)</td>
<td>Hematuria, Irritation</td>
<td>TUR</td>
<td>65</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>M 68</td>
<td>Bladder</td>
<td>LC (κ=λ)</td>
<td>Hematuria, Irritation</td>
<td>TUR</td>
<td>24</td>
<td>No</td>
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<tr>
<td>7</td>
<td>M 60</td>
<td>Bladder &amp; urethra</td>
<td>LC (λ&gt;κ)</td>
<td>Hematuria, mass</td>
<td>TUR</td>
<td>146</td>
<td>No</td>
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<tr>
<td>8</td>
<td>M 60</td>
<td>Ureter</td>
<td>LC (κ=λ)</td>
<td>Mass, Obstruction</td>
<td>Ureterectomy</td>
<td>92</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>M 76</td>
<td>Ureter</td>
<td>LC (κ=λ)</td>
<td>Hematuria, mass</td>
<td>Ureterectomy</td>
<td>7</td>
<td>No</td>
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<tr>
<td>10</td>
<td>F 77</td>
<td>Renal pelvis</td>
<td>LC (κ&gt;λ)</td>
<td>Hematuria, mass</td>
<td>Nephrectomy</td>
<td>153</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>M 71</td>
<td>Renal pelvis</td>
<td>LC (κ=λ)</td>
<td>Hematuria, mass</td>
<td>Nephrectomy</td>
<td>76</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: F=female; M=male; LC=Immunoglobulin light chain; κ=kappa; λ=lambda; n/a=not available; TUR=transurethral resection

Results

The 11 patients consisted of 7 males and 4 females. The mean age at time of diagnosis was 72 years and the ages ranged from 58 to 89 years. The sites involved by amyloidosis included the following portions of the urinary tract: bladder (n=6), bladder and prostatic urethra (n=1), ureter (n=2), and renal pelvis (n=2). Clinical presentations included hematuria (n=8), urinary irritation (3) and mass effect (8) (Table 1). Urine cytologic evaluation for 5 patients showed no evidence of neoplasia. Radiologic data were available for 6 cases; 2 cases were undetected, while 4 cases showed mass effect and suspicion for neoplasm (Figure 1). In all patients, amyloidosis was diagnosed histologically with the aid of special stains and immunohistochemistry. On hematoxylin-eosin (H & E) stain, the amyloid appeared as eosinophilic amorphous deposits in the sub-urothelial lamina propria and extended into the connective tissue surrounding muscle fascicles (Figures 2A and 3A). With Congo Red stain it appeared amorphous and pink-red on light microscopy and had apple green birefringence on polarized light microscopy (Figures 2B, 2C and 3D). Amyloid characterization performed on 8 cases showed light chain deposits (Figure 3D). The majority of the cases involving the bladder were treated by transurethral resection. The ureter and renal pelvis cases were treated by surgical resection. The available follow-up data showed an indolent course. Over a mean follow-up time of 73.6 months, with only one exception, there was no evidence of systemic disease, or systemic plasma cell dyscrasia. Serum free light chains, immunofixation electrophoreses and protein electrophoreses were unremarkable. Nine patients remained alive. The two patients who died were both over the age of 85, had been diagnosed at ages 77 & 82, and were at...
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30 months and 153 months after diagnosis, respectively.

One patient (case 1) with bladder amyloidosis had plasma cells with kappa light chain restriction infiltrating the amyloid, mixed with nonclonal B and T lymphocytes, in a background of chronic cystitis. It was diagnosed at an outside institution as a “plasmacytoma” 6 months after our diagnosis of localized amyloidosis of the urinary bladder. Serum electrophoresis showed no abnormality. The patient remains alive at 64 months with management by observation only. This case is included in this study for being diagnosed at our institution as isolated amyloidosis.

Discussion

The cause of primary localized UTA is unknown, although it is postulated that it may result from chronic or recurrent mucosal and submucosal inflammation, as part of chronic cystitis [4, 5]. The infiltrating plasma cells can secrete an aberrant type of amyloidogenic immunoglobulin light chain (kappa, lambda or both), that forms amyloid fibrils and is deposited in the urinary tract. Primary localized UTA is rare and more commonly seen in males whereas chronic cystitis is common and usually seen in females. Other unknown factors must play roles in the development of this disease.

Primary localized UTA typically presents clinically as gross painless hematuria and urinary irritative symptoms that mimic inflammation and neoplasia. Cystoscopic and radiologic findings are usually indeterminate and suggestive of a neoplastic process [6]. Clinical diagnosis of localized UTA is difficult and is usually not suspected in these patients based on the clinical, endoscopic and radiologic appearances.

Figure 2. Microscopic findings of ureter amyloidoma (case 9). Amorphic and eosinophilic amyloid deposits with giant cell reaction (H & E stains, 200x magnification) (A). The deposition appears purple-violet with crystal violet stain (B), amorphous and pink-red with Congo Red stain on light microscopy, and has apple green birefringence on polarized light microscopy (C and D).
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Therefore, physicians should be aware of this entity and should consider it in the differential diagnosis for patients with hematuria and a mass lesion, especially when no other causes for the mass are identified. Whenever possible, urinary tract masses should be evaluated microscopically, either by cystoscopic biopsy or by surgical biopsy with frozen section evaluation, prior to radical resection. Urine cytology is of limited utility since most deposits are subepithelial. Awareness of the existence of localized, isolated UTA with its benign prognosis is important to avoid unnecessary resection. Histological examination with the aid of confirmatory special stains including Congo Red usually provides the correct diagnosis. However, one should be aware that the features of amorphous and eosinophilic amyloid deposits with giant cell reaction on frozen section may mimic malignant cells in a background of tumor necrosis.

Among our cases, the bladder was the most common site of involvement, followed by ureter, urethra, and renal pelvis; this is comparable to previous reports in the literature [4]. Kappa type and lambda type light chains are present in similar proportions in our case series; this is also consistent with previous reports of localized amyloidosis. This ratio is different from systemic amyloidosis, in which lambda type light chains are 2 to 3 times more common than kappa type chains [4, 7]. It is unclear why the ratio of kappa and lambda type light chains is different for the two types of amyloidosis.

Although recurrence uncommonly does occur, primary localized amyloidosis generally has a benign clinical course and usually is cured by complete resection [3, 8]. All of our patients with biopsy-diagnosed bladder and urethral amyloidosis were managed by observation or local resection. All alive with no recurrence.

Figure 3. Microscopic findings of bladder amyloidoma (case 7). Eosinophilic amorphous amyloid material deposits in the sub-urothelial lamina propria and the connective tissue surrounding muscle fascicles (A). The amyloid protein appears amorphous and pink-red with Congo Red stain on light microscopy and shows apple green birefringence on polarized light microscopy (B and C). The amyloid proteins are Immunoglobin light chain κ and λ. Immunostain of Immunoglobin light chain λ (D).
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except one patient who died after 30 months from stroke (case 3). The two patients with ureteral involvement were treated by ureterectomy and were both alive with no recurrence. One with renal pelvis involvement, diagnosed at 77, was treated with nephrectomy and died after 12 years and 9 months, of unknown cause.

In summary, despite the rarity of localized amyloidosis, urologists, radiologists and pathologists should be aware of this entity to avoid misinterpretation and overtreatment. Histological examination is a requirement for definitive diagnosis and proper management. When diagnosis of AL amyloidosis is made, it is important to pursue further work-up to evaluate for systemic amyloidosis. Primary localized amyloidosis has a benign clinical course and usually is cured by with complete resection.

Disclosure of conflict of interest

None.

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References


