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Primary Amyloidosis of the Genitourinary Tract

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- **Context.**—Amyloidosis is caused by the deposition of misfolded proteins as insoluble eosinophilic material in the extracellular tissues of the body, leading to impairment of organ function. It can be systemic or localized. Localized genitourinary tract amyloidosis is rare and can be incidentally seen; however, in some cases, it can be the only presenting disease.

  **Objective.**—To review the clinical presentation and pathologic findings related to primary amyloidosis of the urogenital system and highlight some of the associated pathologic findings based on our personal experience.

**Data Sources.**—Published peer-reviewed literature and personal experience of the senior author.

**Conclusions.**—Primary localized amyloidosis within the urogenital tract can present as a neoplastic process and may be clinically and radiologically considered as a mass. Awareness of primary amyloidosis by pathologists and clinicians is required for accurate diagnosis and proper patient management.

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Amyloidosis is a heterogeneous group of disorders caused by the deposition of misfolded proteins in the extracellular tissues. These misfolded proteins are formed of different amino acid peptides that share a common backbone of β-sheet conformation. This renders them insoluble and resistant to proteolytic activity. Based on the amino acid composition, the form of the amyloid deposit varies in severity and organ involvement. To date, more than 25 proteins have been described to be amyloidogenic, all of which are indistinguishable by light or electron microscopic examination.

Amyloidosis can be classified based on the type of amyloidogenic protein or based on tissue distribution. The accumulation of the insoluble amyloidogenic fibrils in the extracellular tissue can be hereditary or acquired, as well as systemic or localized. It can lead to disruption and functional impairment of the involved organ(s) or can be asymptomatic. Localized amyloidosis accounts for 10% to 20% of cases. It can be seen in many organs, including the skin, soft tissues, genitourinary system, respiratory system, gastrointestinal tract, and lymph nodes. In the urinary tract, it is rare and most commonly seen incidentally in prostatectomy specimens within the seminal vesicles. Because of its nonspecific clinical and radiologic findings, the diagnosis of amyloidosis requires examination of tissue specimens.

The etiology of localized amyloidosis is unknown. It has been postulated that recurrent chronic inflammation with associated migration of lymphoplasmycytic cells may result in an aberrant monoclonal proliferation and local secretion of light chains. These light chains may then accumulate and transform into amyloid by lysosomal degradation.

This review will highlight the clinical presentations and pathologic findings related to primary amyloidosis in each organ of the urinary tract system. This will also include highlights of unusual associations based on our institutional experience.

**DIAGNOSIS OF AMYLOIDOSIS**

Radiologically, there is no specific finding to detect amyloidosis; however, some radiologic reports indicate that amyloidosis should be suspected when the lesion is visualized as a hypointensity on T2-weighted magnetic resonance images and no obvious mass is appreciated, whereas others consider the presence of calcifications as a typical computed tomography scan sign of amyloidosis, despite its being nonspecific and appearing in many other conditions.

The definitive diagnosis of amyloidosis requires histologic examination. Microscopically, amyloidosis deposits in the tissue as an extracellular pink, homogenous, amorphous, and acellular material. Although its appearance may suggest the diagnosis, the presence of amyloidosis requires confirmatory testing by special histochemical stains. Congo red stain, which typically renders amyloid deposits a salmon-pink color, is the most commonly used stain for its detection. Despite this characteristic appearance of Congo red stain, it has to be examined under a polarized light, which shows apple-green birefringent deposits. All amyloid types can be detected by Congo red stain; however, the secondary (amyloid A) type loses the affinity to stain for Congo red when it is pretreated with potassium permanganate. Amyloid detection can also be achieved using immunohistochemical methods. However, this may as well reveal inconclusive results related to epitope characteristics or background staining.
Despite this relatively straightforward diagnosis of amyloidosis, additional subtyping is required for treatment. This subtyping is achieved by laser microdissection, then analysis by liquid chromatography/mass spectrometry technology. This methodology has its value in confirming the diagnosis as well as subtyping based on the peptide composition of the amyloidogenic protein with high sensitivity and specificity.17

**PRIMARY AMYLOIDOSIS OF THE KIDNEY**

The kidney is the most frequently involved organ in the genitourinary tract system. The estimated prevalence of renal amyloidosis is 2% to 3% in renal biopsies, most commonly of amyloid light-chain or amyloid A types.5,38 When symptomatic, patients present with a variable degree of proteinuria, ranging from subnephrotic to massive proteinuria, along with other features of nephrotic syndrome. The severity of symptoms depends on multiple factors, including the intrarenal distribution of the deposits. For instance, amyloid light-chain amyloidosis most commonly has a glomerular deposit and presents with proteinuria in up to 75% of patients, whereas amyloid A is commonly reported in crescentic glomerulonephritis. Imaging is nonspecific and may show normal or enlarged kidneys.19–23 To date, a single case of primary localized (amyloid light-chain) renal amyloidosis has been reported by Fuah and Lim24 in a 53-year-old male patient who presented with proteinuria.

Microscopically, amyloid deposition can be glomerular, interstitial, tubular, or vascular, with or without associated renal lesions.28 In a proposed classification by Shen and Sarsik,26 renal amyloidosis was classified into 7 histomorphologic classes (0–VI), including no amyloid deposition, minimal (<10%) focal or segmental deposition in the mesangium or vascular pole, mesangial minimal (10%–25%), focal mesangiocapillary amyloid deposition (26%–50%), diffuse mesangiocapillary deposition (51%–75%), membranous amyloid deposition, and advanced amyloidosis.

Despite attempts to unify the histomorphologic classification, the relationship between degree and pattern of renal pathologic involvement and clinical outcome is still unclear. Slowly progressive chronic kidney disease is seen in patients with vascular and tubular amyloidosis. However, by far, glomerular deposit appears to be the most important factor determining clinical outcome, especially when proteinuria is accompanied by other features of nephrotic syndrome.25,27 Additionally, intratubular amyloid precipitation (amyloid cast) has recently been described as a risk factor for systemic light chain amyloidosis and may result in acute kidney injury.5,22

**PRIMARY AMYLOIDOSIS OF THE URETER**

In the ureter, amyloidosis is rare and mostly published as case reports.28 It occurs predominantly in females, with a female to male ratio of 1.9:1. The mean age at diagnosis is 58 years (range, 17–81 years) and the majority of patients present with flank pain, followed by hematuria.13 In a report by Ding et al,28 up to 60% of ureteric involvement was seen in the lower ureter, followed by the upper portion.

An unusual association between localized ureteric amyloidosis and nephrogenic adenoma was noted in one of the lesions identified in our institution. The ureteric lumen was circumferentially narrowed by an acellular hyaline material, admixed with numerous variably sized (PAX-8 positive) tubules in a background of abundant lymphoplasmacytic inflammation. The acellular hyaline material had a salmon-pink color on Congo red stain and showed apple-green birefringence on polarization (Figures 1, A through D, and 2, A and B). This had formed a polypoid mass that further obstructed the ureteral lumen. It is unclear which lesion antedates the other, but the chronic and recurrent inflammation may have led to localized amyloidosis with subsequent trapping of renal tubular cells and the development of nephrogenic adenoma, further complicating the ureteric obstruction.

**PRIMARY AMYLOIDOSIS OF THE URINARY BLADDER**

Primary localized amyloidosis within the urinary bladder occurs commonly in older men (mean age, 55 years), and most patients present with gross hematuria, urinary irritation, or urinary obstructive symptoms.29,30 It mostly involves the posterior wall, followed by the dome of the bladder, in either single or multiple distributions.29 The bladder may appear normal on cystoscopic examination, may show multiple edematous areas, or may show a solid lesion. Additionally, it is not uncommon for localized amyloidosis to present as a neoplastic process with a mass effect mimicking malignancy.31–34 Imaging characteristics are also nonspecific and may show a mass lesion, thickening of the bladder wall, or areas of calcifications.34,35 This presentation may lead to transurethral resection of the bladder. Microscopically, amyloidosis is seen in the lamina propria as an abundant hyalinized, acellular extracellular material. The surface urothelium is benign and may show reactive changes. A Congo red histochemical stain should show salmon–pink color and gives an apple–green birefringence on polarization.

Fibromyxoid nephrogenic adenoma is a benign lesion that should be considered in the differential diagnosis of amyloidosis, especially in the urinary bladder. It appears as compressed tubules and spindled cells in a prominent fibromyxoid eosinophilic extracellular matrix.36 In these cases, PAX-8 immunostain is helpful to establish the diagnosis.37 Plasmacytoid urothelial carcinoma may also have a similar cystoscopic appearance to amyloidosis. The mucosa in this lesion may appear normal or edematous with no surface lesions. Histologically, the tumor cells are discohesive, have a plasmacytoid appearance, and are seen infiltrating into an edematous and myxoid stroma. An associated high-grade urothelial carcinoma component is usually seen in these cases.38

Primary amyloidosis of the urinary bladder has a high recurrence rate, reaching 54% as reported by Tirzaman et al,29 although many patients may remain free of recurrence for an extended period of time.

**PRIMARY AMYLOIDOSIS OF THE PROSTATE AND SEMINAL VESICLES**

Primary amyloidosis of the prostate is extremely rare, with fewer than 10 cases reported in the English-language literature. It was found in up to 1.5% of prostatectomies (n = 4 of 262) as reported by Lupovitch.39 In the patients with predisposing systemic conditions such as multiple myeloma, Wilson et al40 reported that as many as 47% of prostates were involved by amyloidosis. The increasing trend toward prostatic biopsies is expected to affect this incidence over time, although no updated incidence reports

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are available. On examination, patients may present with prostatic nodularity and usually have increased serum prostate-specific antigen levels, most likely due to an associated inflammation. Microscopically, amyloid deposition is seen mostly in the stroma and sometimes around the blood vessels. More commonly, amyloidosis is seen to affect the seminal vesicles. This represents the second most common urinary organ to be involved by amyloidosis, after the kidneys. Amyloidosis of seminal vesicles and ejaculatory ducts is incidental in the vast majority of cases, and the diagnosis is made on prostatectomy specimens performed for prostatic adenocarcinoma. It is estimated that the seminal vesicle and ejaculatory ducts are involved by amyloidosis in up 16% of autopsy series and 1.1% to 4.7% of resected prostatectomy specimens.

Imaging studies of seminal vesicles may show low-signal intensity mimicking neoplastic involvement by adenocarcinoma. This may affect treatment decisions in patients with prostatic adenocarcinoma, as it can be interpreted as prostatic carcinoma extension into the seminal vesicles. Microscopically, amyloidosis often involves the seminal vesicles bilaterally, in a subepithelial distribution with variable luminal compression and narrowing. Vascular and muscular involvement are usually absent, probably explaining the lack of functional impairment and symptomatic presentation.

**PRIMARY AMYLOIDOSIS OF THE TESTIS AND PARATESTICULAR TISSUE**

Testicular involvement by amyloidosis is extremely rare, and all reported cases were results of secondary involvement by systemic amyloidosis. No primary localized amyloidosis of the testicular adnexa has been reported to date.

**SUMMARY**

Amyloidosis of the genitourinary tract is a rare disease that may mimic a neoplastic process both clinically and radiologically. A higher level of awareness of this entity is required by pathologists and clinicians for accurate diagnosis and patient management.
Figure 2. A and B, The amorphous hyaline material showing salmon-pink color on Congo red stain and apple-green birefringence on polarization, respectively (original magnification ×100).

References

1. Mollee P, Renaut P, Gottlieb D, Goodman H. How to diagnose amyloidosis. Intern Med J. 2014;44(1):7–17.
2. Rambaran RN, Serpell LC. Amyloid fibrils: abnormal protein assembly. Prion. 2008;2(3):112–117.
3. Sunde M, Serpell LC, Bartlam M, Fraser PE, Pepys MB, Blake CC. Common core structure of amyloid fibrils by synchrotron X-ray diffraction. J Mol Biol. 1997;273(3):729–739.
4. Westermarck P, Benson MD, Buxbaum JN, et al. A primer of amyloid nomenclature. Amyloid. 2007;14(1):179–183.
5. Dember LM. Amyloidosis-associated kidney disease. J Am Soc Nephrol. 2006;17(12):1458–1471.
6. Pepys MB. Pathogenesis, diagnosis and treatment of systemic amyloidosis. Philos Trans R Soc Lond B Biol Sci. 2001;356(1406):203–210; discussion 210–211.
7. Vrana JA, Gamez JD, Madden BJ, Theis JD, Bergen HR, 3rd, Dogan A. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic analysis in clinical biopsy specimens. Blood. 2009;114(24):4957–4959.
8. Scott PP, Scott WW Jr, Siegelman SS. Amyloidosis: an overview. Semin Roentgenol. 1986;21(2):103–112.
9. Biewend ML, Menke DM, Calamia KT. The spectrum of localized amyloidosis: a case series of 20 patients and review of the literature. Amyloid. 2006;13(1):135–142.
10. Monge M, Chauveau D, Cordier C, et al. Localized amyloidosis of the genitourinary tract: report of 5 new cases and review of the literature. Medicine (Baltimore). 2011;90(3):212–222.
11. Weiwei Z, Yi H, Jinsong Z. Primary localized amyloidosis of the ureter. Abdom Imaging. 2011;36(5):609–611.
12. Tsujioka Y, Jinzaki M, Tanimoto A, et al. Radiological findings of primary localized amyloidosis of the ureter. J Magn Reson Imaging. 2012;35(2):431–435.
13. Kawashima A, Allemann WG, Takahashi N, Kim B, King BF Jr, LeRoy AJ. Imaging evaluation of amyloidosis of the urinary tract and retroperitoneum. Radiographics. 2011;31(6):1569–1582.
14. Picken MM. Amyloidosis—where are we now and where are we heading? Arch Pathol Lab Med. 2010;134(4):545–551.
15. Lawrentschuk N, Pan D, Stillwell R, Bolton DM. Implications of amyloidosis on prostatic biopsy. Int J Urol. 2010;11(10):925–927.
16. Wright JR, Calkins E, Humphrey RL. Potassium permanganate reaction in amyloidosis: a histologic method to assist in differentiating forms of this disease. Lab Invest. 1977;36(3):274–284.
17. Holub D, Flodrova P, Pika T, Flofr P, Hajduch M, Dzubak P. Mass spectrometry amyloid typing is reproducible across multiple organ sites. Biomed Res Int. 2019;2019:369891.
18. Davison AM. The United Kingdom Medical Research Council’s glomerulonephritis registry. Contrib Nephrol. 1985;48:24–35.
19. Kyle RA, Greipp PR. Amyloidosis (AL): clinical and laboratory features in 229 cases. J Clin Oncol. 1985;3(10):665–683.
20. Moroni G, Banti G, Maccario M, Meregalli M, Ponticelli C. Extracapillary glomerulonephritis and renal amyloidosis. Am J Kidney Dis. 1996;28(5):695–699.
21. Westermarck GT, Sletten K, Crubel A, Westermarck PA. AA-amyloidosis: tissue component-specific association of various protein AA subspecies and evidence of a fourth SAA gene product. Am J Pathol. 1990;137(2):377–383.
22. Gibier JR, Gennemi V, Glowacki F, et al. Intratubular amyloid in light chain cast nephropathy is a risk factor for systemic light chain amyloidosis. Mod Pathol. 2018;31(3):452–462.
23. Leung N, Kyle RA, Appel GB. Renal amyloidosis. In: Post TW, ed. UpToDate. Waltham, MA: UpToDate; 2019.
24. Fuah KW, Lim CTS. Renal-limited AL amyloidosis—a diagnostic and management dilemma. BMC Nephrol. 2018;19(1):307.
25. Castano E, Palmer MB, Vignau T, Luciano R, Wong S, Moeckel G. Comparison of amyloid deposition in human kidney biopsies as predictor of poor patient outcome. BMC Nephrol. 2015;16:64.
26. Šen S, Sarsik B. A proposed histopathologic classification, scoring, and grading system for renal amyloidosis: standardization of renal amyloid biopsy report. Arch Pathol Lab Med. 2010;134(4):532–544.
27. Kendi Celebi Z, Kiremitci S, Ozturk B, et al. Kidney biopsy in AA amyloidosis: impact of histopathology on prognosis. Amyloid. 2017;24(3):176–182.
28. Ding X, Yan X, Ma X, et al. Localized amyloidosis of the ureter: a case report and literature review. Can Urol Assoc J. 2013;7(11-12):E764–E767.
29. Tirzaman O, Wahner-Roedler DL, Malek RS, Sebo TJ, Li CY, Kyle RA. Primary localized amyloidosis of the urinary bladder: a case series of 31 patients. Mayo Clin Proc. 2007;82(7):1264–1268.
30. Chan ES, Ng CF, Chui KL, Hou SM, Yip SK. Primary bladder amyloidosis—case report of a patient with delayed upper urinary tract obstruction 3 years after the diagnosis. Amyloid. 2010;17(1):36–38.
31. Karan SC, Shah AK, Srivastava A, Bhardwaj R. Primary amyloidosis of urinary bladder: mimicking transitional cell carcinoma bladder! Med J Armed Forces India. 2016;72(1):91–93.
32. Bayrak O, Bozdag Z, Urgun G, Yagi F. Primary amyloidosis of the bladder mimicking bladder tumor. Turk J Urol. 2014;40(1):59–61.
33. Semanriaga Ruiz de la Ibaña N, Loizaga Iríarte A, Lacasa Viscasillas I, Urdab Urzaiz M. Bladder amyloidosis: a lesion that simulates a tumor [in Spanish]. Actas Urol Esp. 2010;34(9):820–821.
34. Ho A, Davies MC, Guran R, Brewin J. Primary amyloidosis of the bladder. Urol Case Rep. 2018;17:111–113.
35. Patel P, Poumendi M, Lombard JS. Primary amyloidosis of the bladder mimicking probable malignancy: a case report. Urol Case Rep. 2019;26:100944.
36. Hansel DE, Nadasdy T, Epstein JI. Fibromyxoid nephrogenic adenoma: a newly recognized variant mimicking mucinous adenocarcinoma. Am J Surg Pathol. 2007;31(8):1231–1237.
37. Pina-Oviedo S, Shen SS, Truong LD, Ayala AG, Ro JY. Flat pattern of nephrogenic adenoma: previously unrecognized pattern unifying used PXA2 and PXA8 immunohistochemistry. Mod Pathol. 2013;26(6):792–798.
38. Humphrey PA, Moch H, Kubilla AL, Ullbright TM, Reuter VE. The 2016 WHO classification of tumours of the urinary system and male genital organs—part B: prostate and bladder tumours. Eur Urol. 2016;70(1):106–119.
39. Lupovitch A. The prostate and amyloidosis. J Urol. 1972;108(2):301–302.
40. Wilson SK, Buchanan RD, Stone WJ, Khamy RK. Amyloid deposition in the prostate. J Urol. 1973;110(3):322–323.
41. Tripathi VN, Desautels RE. Primary amyloidosis of the urogenital system: a study of 16 cases and brief review. J Urol. 1969;102(1):96–101.
42. Park HS, Cho HY. Amyloidosis of the urogenital system. Korean J Urol Oncol. 2010;8(2):59–64.
43. Coyne JD, Kealy WF. Seminal vesicle amyloidosis: morphological, histochemical and immunohistochemical observations. Histopathology. 1993;22(2):173–176.

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44. Pitkanen P, Westermark P, Cornwell GG 3rd, Murdoch W. Amyloid of the seminal vesicles: a distinctive and common localized form of senile amyloidosis. *Am J Pathol*. 1983;110(1):64–69.

45. Rath-Wolfson L, Bubis G, Shtrasburg S, Shvero A, Koren R. Seminal tract amyloidosis: synchronous amyloidosis of the seminal vesicles, deferent ducts and ejaculatory ducts. *Pathol Oncol Res*. 2017;23(4):811–814.

46. Kee KH, Lee MJ, Shen SS, et al. Amyloidosis of seminal vesicles and ejaculatory ducts: a histologic analysis of 21 cases among 447 prostatectomy specimens. *Ann Diagn Pathol*. 2008;12(4):235–238.

47. Jager GJ, Ruijter ET, de la Rosette JJ, van de Kaa CA. Amyloidosis of the seminal vesicles simulating tumor invasion of prostatic carcinoma on endorectal MR images. *Eur Radiol*. 1997;7(4):552–554.

48. Stephens M, Kim DI, Shepherd B, Gustafson S, Thomas P. Intense uptake in amyloidosis of the seminal vesicles on 68Ga-PSMA PET mimicking locally advanced prostate cancer. *Clin Nucl Med*. 2017;42(3):147–148.

49. Corvino C, Balloni F, Meliani E, Giannini A, Serni S, Carini M. Testicular amyloidosis. *Urol Int*. 2002;69(2):162–163.

50. Casella R, Nudell D, Cozzolino D, Wang H, Lipshultz LI. Primary testicular amyloidosis mimicking tumor in a cryptorchid testis. *Urology*. 2002;59(3):445.