Urology Case Reports 39 (2021) 101811

Contents lists available at ScienceDirect

Urology Case Reports

journal homepage: www.elsevier.com/locate/eucr

Gross hematuria: An unusual presenting symptom of systemic wild-type transthyretin amyloidosis

Sage A. Vincent [a], Daniel Christensen [b], Perry R. Weiner [a,*]

[a] Department of Urology, Thomas Jefferson University Hospital. Philadelphia, PA, USA
[b] Department of Pathology, Anatomy & Cell Biology, Thomas Jefferson University Hospital. Philadelphia, PA, USA

ARTICLE INFO

Keywords:
Bladder amyloid
Transthyretin amyloidosis
Gross hematuria

ABSTRACT

Amyloidosis of the urinary bladder is a rare cause of gross hematuria. In patients with systemic amyloidosis, identification is nearly always related to cardiac complaints; urologic presenting symptoms are extremely uncommon. We present a 77-year-old male patient with painless gross hematuria ultimately found to be secondary to systemic wild-type transthyretin amyloidosis. He underwent transurethral resection of the bladder lesion and was initiated on transthyretin stabilizing medication. In the 6 months since starting treatment, the patient has had no further episodes of gross hematuria, but will require cystoscopic surveillance for evidence of recurrence or concomittment urothelial carcinoma.

1. Introduction

Amyloidosis is a disease characterized by the misfolding of proteins and extracellular deposition of insoluble fibrils in various tissues. The deposition site of these proteins is variable and accounts for the heterogeneous symptomatology. More than 30 distinct misfolded proteins have been identified, the most common of which are transthyretin (ATTR) and light-chain (AL) amyloid.[1] Amyloid deposition can occur locally, impacting one discrete organ, or systemically, with the latter associated with poorer prognosis and more severe quality of life impacts.

It is known that the bladder can be involved in systemic ATTR amyloidosis, though the incidence of this phenomenon is unknown. It is exceedingly rare and there is a scarcity of literature in which urologic symptoms prompt a work-up and eventual diagnosis of systemic ATTR amyloidosis. No guidelines regarding management and follow-up of bladder amyloidosis exist.

Described here is a patient presenting with gross hematuria who was found to have systemic ATTR amyloidosis.

2. Case presentation

A 77-year-old male with past medical history of chronic myelogenous leukemia (CML) stable on imatinib, dilated cardiomyopathy thought to be related to previous nilotinib treatment, carpal tunnel syndrome, lumbar stenosis and no tobacco history presented to the emergency department with gross hematuria. His urine showed large blood and was negative for leukocyte esterase and nitrites. His hemoglobin was 12.0, stable from prior, and his coagulation labs were normal. Non-contrast CT scan of the abdomen and pelvis revealed bilateral non-obstructing lower pole stones with no evidence of hydronephrosis and a mildly thickened bladder wall, which was attributed to prostatic hypertrophy.

The patient reported to the outpatient urology clinic, where office cystoscopy showed a questionable lesion with adherent clot on the posterior wall of the bladder as well as adjacent cobblestoned mucosa and diffuse trabeculations. Urine cytology was negative for malignancy. The patient underwent a transurethral resection of bladder tumor during which a resectoscope was introduced and the lesion was widely excised with adequate hemostasis. Pathology report showed acellular, eosinophilic deposits in the lamina propria (Fig. 1). Congo red stain was positive and demonstrated apple green birefringence under polarized light (Fig. 2), suggestive of a diagnosis of amyloid. The sample was sent for liquid chromatography tandem mass spectrometry (LC MS/MS) which revealed peptide sequences consistent with ATTR amyloid. Genetic testing did not show any mutations in ATTR proteins, suggestive of wild-type amyloidosis.

Plasma cell dyscrasias were ruled out biochemically, including normal urine protein electrophoresis (UPEP), serum protein electrophoresis (SPEP) and free serum light chains. No evidence of gastrointestinal, liver or kidney involvement was found. In light of the patient's

* Corresponding author. 3 Crescent Drive, Suite 100, Philadelphia, PA, 19112, USA.
E-mail address: Perry.Weiner@jefferson.edu (P.R. Weiner).

https://doi.org/10.1016/j.eucr.2021.101811
Received 25 July 2021; Accepted 17 August 2021
Available online 18 August 2021

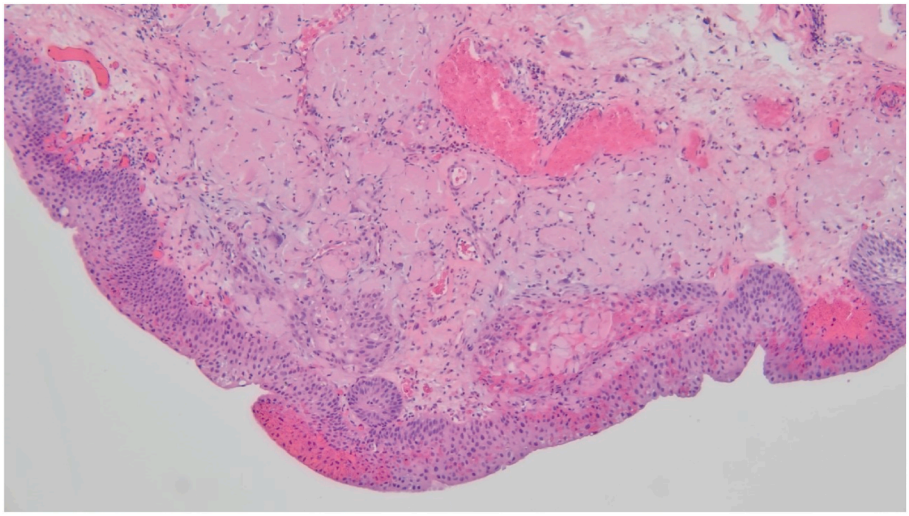

Fig. 1. H&E stain at 100× magnification. Acellular, amorphous eosinophilic material in the lamina propria underlying benign urothelium.

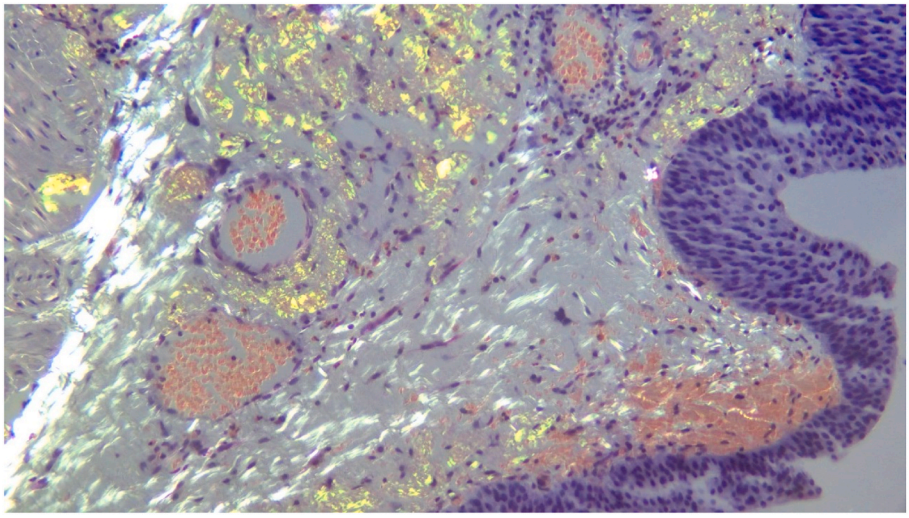

Fig. 2. Congo Red stain at 200× magnification. Acellular, amorphous material staining red orange with apple-green birefringence under polarized light. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

history of dilated cardiomyopathy, the patient underwent additional workup, which revealed characteristic findings of cardiac amyloid deposition including cardiac magnetic resonance imaging (MRI) with circumferential left ventricular hypertrophy, patchy late gadolinium enhancement and failure of the myocardium to null on Look-Locker sequences, as well as cardiac pyrophosphate (PYP) scan with diffuse, 3+ uptake of technetium pyrophosphate.

The patient was initiated on tafamidis therapy for his systemic, wild-type ATTR amyloidosis. In the 6 months since starting treatment, there have been no further episodes of gross hematuria or evidence of worsening left ventricular dysfunction which would indicate additional amyloid deposition.

3. Discussion

Amyloidosis involving the kidneys, ureters, prostate or bladder is incredibly rare. Amyloid lesions in the bladder mimic urothelial carcinoma, both in appearance and presentation, having been described as polypoid, ulcerated and hemorrhagic papules which are found after episodes of painless gross hematuria. Amyloidosis localized to the urinary bladder has been described in less than 200 cases, including the largest case series which highlighted 31 patients with primary localized AL amyloidosis of the urinary tract.[2] Of the patients in the series, 84% were treated with simple resection or fulguration. Localized amyloidosis of the bladder is almost exclusively due to AL amyloid, which is likely related to chronic inflammation and recruitment of monoclonal plasma cells.

Systemic ATTR amyloid may also deposit in the urinary tract, as was seen in the patient presented above. Typical presentation of ATTR amyloidosis includes cardiac symptoms such as palpitations, dyspnea on exertion and edema, as well as noncardiac symptoms like carpal tunnel and spinal stenosis.[1] The pathogenesis of wild-type ATTR amyloidosis is related to aging, in which the precursor proteins lose their ability to fold properly over time.

At present time, there is only one case report documenting the diagnosis of systemic ATTR amyloidosis following an episode of hematuria,[3] with the case above highlighting an additional patient. A high degree of suspicion is necessary to diagnose amyloidosis, as there are many more common causes of hematuria. Early diagnosis and initiation of treatment can reduce continued amyloid deposition, significantly improving all-cause mortality.[1] ATTR amyloid deposition can also cause other urologic complaints, with as many as 83% of patients with

systemic disease reporting LUTS, greater than 40% reporting sexual dysfunction and a third reporting UI,[4] which are thought to be the result of peripheral and autonomic nerve involvement. While it is important to acknowledge that the aging population in general has a high prevalence of these urologic complaints, any suspicion of a secondary cause of a patient's symptoms should not be ignored.

The recurrence rate of bladder amyloidosis is reported to be 54%,[2] indicating the importance of continued urologic monitoring in these patients. More formidable than amyloid recurrence is the association between bladder amyloid and urothelial carcinoma. In a retrospective review, the rate of urothelial carcinoma in patients with known bladder amyloid was 48%, a third of which were high-grade at the time of diagnosis.[5] Histologically, amyloid deposits were seen adjacent to the malignant lesions, never seen within the tumor itself. Surveillance cystoscopy in patients with bladder amyloidosis is therefore recommended to identify local recurrence and possible urothelial carcinomas.

4. Conclusion

This case highlights a rare cause of gross hematuria. It is diagnostically unusual to find amyloid in the bladder and later identify systemic amyloidosis, rather than the reverse. Because this is so uncommon, it requires a high degree of suspicion and continued surveillance due to the likelihood of recurrence and association with urothelial carcinoma.

Consent

Verbal and written informed consent was obtained from the patient for publication of his de-identified clinical information.

Declaration of competing interests

No authors have any conflicts of interest.

Author contributions

Author 1: drafting of the manuscript including case presentation, literature review and discussion.

Author 2: retrieving pathology images, writing pathology description, fact-checking relevant manuscript sections.

Author 3: revision and editing of the manuscript, supervision, conceptualization.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Gertz MA, Dispenzieri A. Systemic amyloidosis recognition, prognosis and therapy. *J Am Med Assoc*. 2020;324(1):79–89. https://doi.org/10.1001/jama.2020.5493.
2. 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*. 2000;75:1264–1268. https://doi.org/10.4065/75.12.1264.
3. Jayakrishnan T, Kamran A, Shah D, Guha A, Faisal MS, Mewawalla P. Senile systemic amyloidosis presenting as hematuria: a rare presentation and review of literature. *Case Reports in Medicine*. 2020. https://doi.org/10.1155/2020/5892707.
4. Bentellis I, Amarenco G, Gamé X, et al. Diagnosis and treatment of urinary and sexual dysfunction in hereditary TTR amyloidosis. *Clin Auton Res*. 2019;29(Suppl1):65–74.
5. Sirohi D, Gandhi J, Amin MB, Luthringer DJ. Amyloidosis of the bladder and association with urothelial carcinoma: report of 29 cases. *Hum Pathol*. 2019;93:48–53. https://doi.org/10.1016/j.humpath.2019.08.011.