ACTAS UROLÓGICAS ESPAÑOLAS

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Short original – Inflammation-infection

Secondary amyloidosis of the bladder and massive hematuria

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ARTICLE INFORMATION

Article history:
Received on 1 September 2008
Accepted on 26 October 2009

Keywords:
Secondary amyloidosis
Urinary bladder
Massive hematuria

A B S T R A C T

Objective: To report four additional cases of secondary amyloidosis of the bladder, an extremely rare condition, as shown by the cases reported in the literature.
Materials and methods: Four clinical cases are reported, all of them occurring as hematuria, which was massive and fulminant and resulted in death in three patients.
Results: Secondary amyloidosis of the bladder is of the AA type, which is more common in females and mainly secondary to rheumatoid arthritis, but also to ankylosing spondylitis and long-standing chronic inflammatory conditions. Hematuria is the main and virtually only symptom. A pathological and immunohistochemical study confirmed diagnosis. All three patients who experienced massiva, fatal hematuria had an intercurrent condition requiring urethral catheterization, which was the triggering factor.
Conclusions: Despite its rarity, as shown by the few cases reported, secondary amyloidosis of the bladder should be considered in patients already diagnosed with systemic amylodosis and/or the conditions reported who require simple urethral catheterization.

Amiloidosis vesical secundaria y hematuria masiva

Palabras clave:
Amiloidosis secundaria
Vejiga urinaria
Hematuria masiva

R E S U M E N

Objetivo: Dar a conocer cuatro nuevos casos de amiloidosis vesical secundaria, cuya manifestación clínica es extraordinariamente rara, si atendemos a los escasos casos publicados que no llegan a la treintena.
Material y métodos: Describimos los cuatro casos clínicos, manifestados todos ellos por hematuria, siendo en tres masiva y fulminante, con evolución fatal.
Resultados: La amiloidosis vesical secundaria corresponde al tipo AA, más frecuente en mujeres y secundaria sobre todo a artritis reumatoide, pero también a espondilitis anquilopoyética y procesos inflamatorios crónicos de larga evolución. La hematuria es el síntoma fundamental, prácticamente único. El estudio patológico e inmunohistoquímico

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0210-4806/$ - see front matter

confirma el diagnóstico. Se da la circunstancia de que los tres casos de hematuria masiva y fatal presentaron una patología intercurrente que precisó practicar un sondaje uretral, siendo éste el desencadenante.

Conclusiones: A pesar de su rareza, confirmada por los pocos casos publicados, habrá que pensar en ella ante pacientes ya diagnosticados de amiloidosis sistémica y/o con las patologías descritas, que precisen un simple sondaje uretral.

Introduction

Amyloidosis, initially described by Rokitansky, received its name from Wirchov, who in 1853 coined the term in reference to the staining similarities with starch[1]. Amyloidosis comprises a group of conditions characterized by the extracellular accumulation of insoluble fibrillar proteins referred to as amyloid, in quantities sufficient to cause impaired function of the affected tissues[2].

Depending on the affected organs, the disease can be classified as localized or systemic, while on the basis of the biochemical characteristics and origin of the accumulated fibrillar proteins, three main types of amyloidosis storage disease have been established: the first is referred to as AL amyloidosis, and corresponds to primary amyloidosis; the second is AA amyloidosis and is found in patients with secondary presentations of the disease; and the third is AF amyloidosis, which is associated to familial amyloid polyneuropathy. There are two additional types, known as senile amyloidosis (AS) and hemodialysis-related amyloidosis (AB2-M).

In primary amyloidosis (AL) there is no evidence of associated diseases except multiple myeloma, and the most affected organs are the heart and vascular system, the lungs, skin, tongue, thyroid gland and gastrointestinal tract.

In secondary amyloidosis (AA), the preferential accumulation sites are the spleen, liver, kidneys, adrenal glands and lymph nodes. As suggested by the name of the disease, amyloidosis is related to chronic inflammatory processes secondary to long-evolving conditions such as chronic infection (bronchiectasis, tuberculosis, chronic osteomyelitis, etc.) and rheumatological disorders (rheumatoid arthritis, ankylopoietic spondylitis, lupus erythematosus, etc.).

Other cases have also been described, however, including specifically a patient with primary and localized bladder amyloidosis presenting with painless macroscopic hematuria and two nodular masses in the bladder evidenced by cystoscopy - the biopsy revealing amyloidosis, with an immunohistochemically-established diagnosis of AA amyloid disease[3].

The histological diagnosis is based on the use of the Congo red stain (fig. 1 A and B), which under the polarization microscope shows the characteristic apple-green birefringence characteristic of amyloid (fig. 2). Histochemically, it is possible to distinguish the different types through treatment with potassium permanganate ($KMnO_4$). The principal deposits (AL) generally persist after permanganate treatment, while in the secondary form of the disease (AA) the deposits are digested[4] (fig. 3). If doubts persist despite the above techniques, immunohistochemical methods (immunoperoxidase) and monoclonal antibodies (MAb Ab-1) can be used[5].

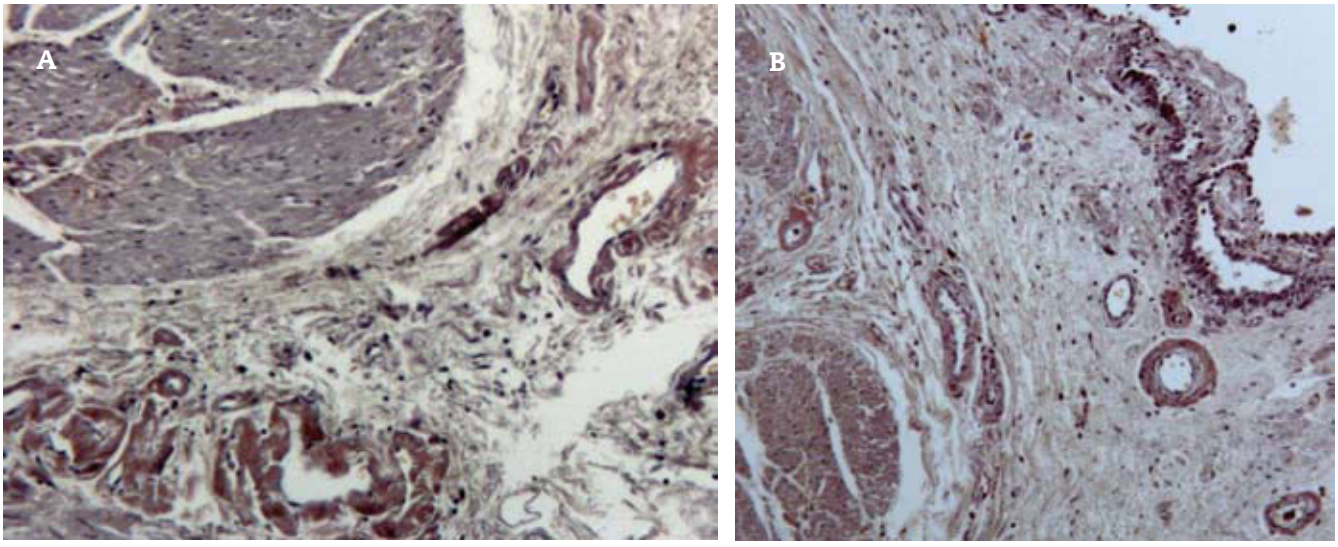

Figure 1 – Congo red staining. Vascular and perivascular involvement.

The present study describes four cases of secondary bladder amyloidosis, all manifesting with hematuria. In three of the cases the presentation was massive and fulminant, with a fatal outcome.

Clinical cases

Case 1

A 53-year-old male was diagnosed with ankylopoietic spondylitis (HLA B27), secondary amyloidosis and end-stage chronic renal failure subjected to hemodialysis. He developed painless hematuria, and cystoscopy revealed the presence of an excrescent but non-papillary and bleeding bladder mass. Transurethral resection (TUR) was carried out, the histological diagnosis being bladder amyloidosis. The course proved satisfactory, though 11 months later the patient was readmitted with intense fixed abdominal epigastric pain. This was followed two hours later by sudden abundant and blood-containing vomiting, which was complicated by cardiorespiratory arrest and led to the death of the patient (11/04/1995). The postmortem histopathological study showed ischemic necrosis of the digestive tract vascularized by the superior mesenteric artery, with amyloid deposits in vessels of the submucosa. There was generalized involvement of body organs and systems, including bilateral renal atrophy due to amyloidosis. Bladder amyloidosis (AA) was established, particularly at perivascular level, together with amyloidosis of the prostatic vessels.

Case 2

A 58-year old woman was diagnosed with stage IV rheumatoid arthritis, secondary amyloidosis, chronic renal failure and arterial hypertension. She was emergency admitted with congestive heart failure. The echocardiographic study revealed mitral valve insufficiency with probable tendinous cord rupture and ultrasound images suggestive of verrucose lesions. With a diagnosis of heart failure secondary to endocarditis, antibiotic and diuretic treatment was started. Urethral catheterization was thus carried out. However, two days later the patient developed intense hematuria causing bladder distension due to a large blood clot as evidenced by ultrasound. Transurethral evacuation of the hematoma was carried out under general anesthesia, revealing global inflammation and bleeding of the bladder mucosa. Multiple biopsies were obtained, with electrocoagulation of the bladder wall. In the immediate postoperative period the patient suffered cardiorespiratory arrest leading to death (30/06/1996). The histopathological diagnosis was bladder amyloidosis (AA).

Case 3

An 84-year-old woman diagnosed with rheumatoid arthritis was emergency admitted due to abdominal bloating and pain. With a diagnosis of subocclusive ileus, clinical management was initially decided. In the absence of urological antecedents, the patient developed hematuria a few hours after the start of urethral catheterization. The hematuria became very intense, with the formation of a large bladder clot occupying the entire organ cavity. In addition, a computed axial tomography scan revealed the presence of perivesical liquid and gas. Emergency surgery was carried out, revealing a 1.5-meter segment of the ileum extending to 10 cm from the ileocecal valve and presenting an edematous purple color. The segment was seen to recover, with normal appearance, color and peristalsis. A small bladder wall fissure was identified. A cystostomy was thus performed, draining the large blood clot. Diffuse bleeding of the wall was observed, and the latter proved highly friable. Multiple biopsies were obtained, followed by ligation of both hypogastric vessels. In the immediate postoperative period, following anuria and severe hemodynamic alterations, the patient died (09/05/2000). The histopathological study showed all bladder biopsies to contain vascular and interstitial amyloid (AA).

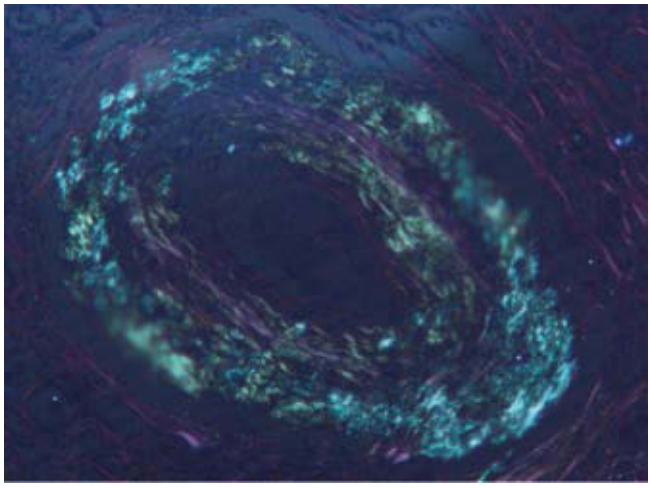

Figure 2 – Apple-green birefringence under the polarization microscope.

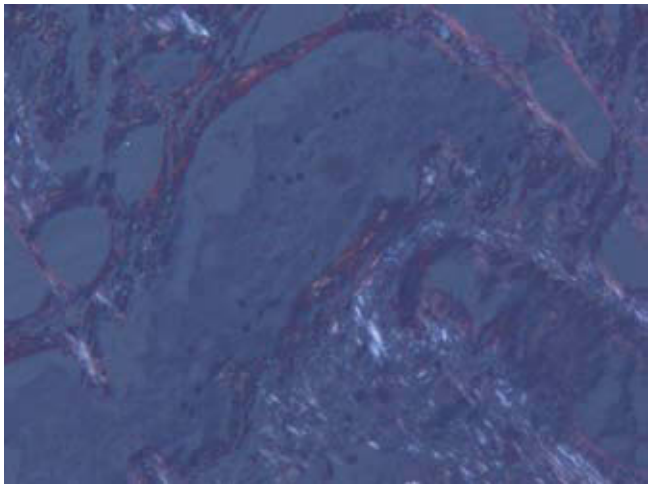

Figure 3 – Disappearance of the secondary amyloidosis deposits with potassium permanganate processing.

Case 4

This case corresponded to a 74-year-old woman who had been admitted on several occasions in the past due to bronchiectasia and peribronchiectasic pneumonitis, multifactorial severe anemia, chronic renal failure, endoscopic signs of diffuse chronic gastritis, and positive rheumatoid factor. As a consequence of an accidental fall, she suffered left humeral fracture and hip fracture on the same side. During admission to Traumatology, the patient developed macroscopic hematuria (post-catheterization), hypotension, febricula, and worsening of her renal function. She was therefore moved to Intensive Care, where she died with the diagnosis of pneumonia evolved to pulmonary abscess, fulminant hematuria, *Pseudomona* sepsis, and acute renal failure (13/07/2004). Previously, as a consequence of the presence of a bladder clot occupying the entire organ cavity, endoscopic drainage had been performed, revealing a denuded and inflamed bladder wall with diffuse bleeding, and no evidence of tumor disease. Multiple biopsies were obtained. The histopathological diagnosis was bladder amyloidosis (AA) with amyloid deposits fundamentally located at perivascular level, but also within the stromal component.

Discussion

The first description of bladder amyloidosis in the world literature was published by Solomin in 1897. As early as 1947, the reputed urologist Luis Cifuentes-Delatte, in his monograph *Cistitis y Cistopatías*, described the disease, and documented 6 cases found in the literature[6].

At urinary tract level, kidney involvement is almost always seen in the context of secondary amyloidosis[4], as in our series, where three patients presented chronic renal failure (one on hemodialysis). In contrast, the bladder is fundamentally affected in the context of localized primary amyloidosis[7-10].

In the review published by Malek in 2002[11], the literature had only contributed 160 cases of localized bladder amyloidosis – though posteriorly several additional cases have appeared, including one in the Spanish literature[12]. The condition is more common in males (71%). The initial manifestations consist of asymptomatic hematuria (58%), irritative lower urinary tract symptoms (20%), and the combination of both (22%). The most common cystoscopic findings are excrescent masses and inflammatory lesions. The biopsies revealed amyloidosis (AL), though as has been commented, a case has been documented in which the immunohistochemical study identified AA amyloidosis.

The rectal and abdominal subcutaneous adipose tissue biopsies prove negative. The most widely used treatments are laser fulguration, TUR and intravesical dimethylsulfoxide (DMSO) instillations[11]. Recurrences are observed in 38% of all cases, and some patients have required cystectomy with urinary bypass procedures[7].

Secondary bladder amyloidosis is curiously less frequent, since no more than 30 cases have been published in the world literature to date. The first case was published by Bender and Nelly in 1969[13]. The largest series to date (5 cases) was published by Nurmi et al. in 1987[14], and massive hematuria was already cited in this series. The reported mortality rate is 30%. In the Spanish literature we have found references to a total of 7 cases[12,15-20]. However, as has been established from necropsy studies of systemic amyloidosis, it is clear that bladder involvement is more common than actual clinical manifestations of the disease[14,15]. Our four cases of secondary bladder amyloidosis agree with the findings in the literature in that women in particular are affected, and rheumatoid arthritis is the most common initial triggering disorder. Two of our patients had already been diagnosed with generalized amyloidosis, and three suffered chronic renal failure at the time of the clinical manifestation of secondary bladder amyloidosis. None of the patients had a history of lower urinary tract symptoms or hematuria.

Hematuria was the initial symptom in all of our patients. This agrees with the data found in the literature, and can be explained by the fact that the amyloid deposits are fundamentally located at vascular and perivascular level within the bladder submucosa – this preventing correct hemostatic vasoconstriction[14,17]. In three of our patients hematuria was massive, fulminant and fatal, and there had been previous intercurrent complications in the form of heart failure due to endocarditis, intestinal obstruction, and fracture of the humerus and hip, respectively. This is in line with the latest cases published in the Spanish literature, involving two cases of traumatologic surgery[19,20] and a case of colon perforation[18]. The ultimate hematuria triggering factor was bladder catheterization, as has already been reported by other authors[17,18,20]. One of our patients presented a small bladder wall fissure that must be attributed to the urethral catheter or to excess pressure caused by the intravesical blood clot and friability of the bladder wall.

Cystoscopically, and unlike in localized primary amyloidosis (AL) which appears as a tumor mass, the most common finding is diffuse inflammation and mucosal ulceration[7], as seen in our three patients with massive hematuria.

As regards treatment, we recorded successful TUR management of a bleeding bladder mass, though failure occurred in the case of massive inflammation and bleeding of the bladder wall, even despite ligation of the hypogastric arteries in one patient. The Mikuliz transurethral technique has been described as a hemostatic option, with good initial results[20]. It is clear that the clinical condition of the patient in most cases precludes aggressive surgical treatment such as cystectomy and bypass procedures.

Conclusions

Although bladder involvement in systemic amyloidosis is more frequent (as established from necropsy studies), its clinical manifestation has been little described in the urological literature to date. Nevertheless, this condition must be taken into account in cases of massive and fulminant hematuria, fundamentally in women, in which some of the following antecedents are observed:

1. A diagnosis of systemic amyloidosis.
2. Long-evolving rheumatological disease, particularly rheumatoid arthritis, but also ankylopoietic spondylitis.
3. Chronic inflammatory disease. In addition, in these cases, we must be very strict and prepared in observing the indications of simple urethral catheterization, since it is the main cause of the clinical manifestations described in patients with secondary bladder amyloidosis.

REFERENCES

1. Begara Morillas F, Silmi Moyano A, Espinosa Fernández B. Amiloidosis vesical en una paciente con sospecha de carcinoma vesical. Arch Esp Urol. 1994;47:176-9.
2. Dhillon V, Woo P, Isenberg D. Amyloidosis in the rheumatic diseases. Ann Rheum Dis. 1989;48:696-701.
3. Akram CM, Al-Marhoon EM, Mathew J, Grant CS, Rao TV. Primary localized AA type amyloidosis of urinary bladder: Case report of rare cause of episodic painless hematuria. Urology. 2006;68:1343.
4. Jain M, Kumari N, Chhabra P, Gupta RK. Localized amyloidosis of urinary bladder: a diagnostic dilemma. Indian J Pathol Microbiol. 2008;51:247-9.
5. Linke RP, Gartner HV, Michels H. High-sensitivity diagnosis of AA amyloidosis using Congo red and immunohistochemistry detects missed amyloid deposits. J Histochem Cytochem. 1995;43:863-9.
6. Cifuentes Delate L. Cistitis y cistopatías. Madrid: Ed. Paz Montalvo; 1947. p. 411.
7. 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;75:1264-8.
8. Auge BK, Haluszka MM. Primary amyloidosis of the urinary bladder. J Urol. 2000;163:1867-8.
9. Huang CY, Shun CT, Huang KH, Chen J, Pu YS. Primary amyloidosis of the urinary bladder. J Formos Med Assoc. 2006;105:164-7.
10. Vicioso Recio L, Jiménez Macías N, Castro León A, Gutiérrez Bueso M, García González I. Amiloidosis primaria localizada de la vejiga. Arch Esp Urol. 1995;48:963-6.
11. Malek RS, Wahner-Roedler DL, Gertz MA. Primary localized amyloidosis of the bladder: experience with dimethyl sulfoxide therapy. J Urol. 2002;168:1018-20.
12. Caballero Giné JM, Borrat Font P, Martí Picas L, Ristol Pont J. Amiloidosis vesical: presentación de dos casos. Actas Urol Esp. 2000;24:413-5.
13. Bender LM, Nelly CH. Secondary amyloidosis of the bladder: a case report. J Urol. 1969;102:60-2.
14. Nurmi MJ, Ekfors TO, Puntala PV. Secondary amyloidosis of the bladder: a cause of massive hematuria. J Urol. 1987;138:44-5.
15. Tesedo cubero J, Ristol RM, Fernández Zuazu J. Hematuria masiva y perforación vesical, complicación de una amiloidosis sistémica. Arch Esp Urol. 1991;44:862-4.
16. Bielsa O, Romero JA, Alcaraz A. Amiloidosis vesical secundaria. Una rara causa de hematuria. Actas Urol Esp. 1990;14:76-7.
17. Sanz Jaka JP, Arrinda Yeregui JM, Mendibil Dakal J. Afectación vesical en la amiloidosis sistémica. Actas Urol Esp. 1988;41:325-8.
18. Palmero Martí JL, Budia Alba S, Arlandis Guzmán S, Benedicto Redón A, Hernández Martí M, Jiménez Cruz JF. Amiloidosis vesical secundaria. Actas Urol Esp. 2004;28:238-42.
19. Gómez García I, González Chamorro F, Fernández Fernández E, Palacio España A, Molina Burgos R, Álvarez E, et al. Hematuria y fracaso renal agudo como debut de amiloidosis vesical secundaria. Presentación de un nuevo caso y revisión de la literatura. Actas Urol Esp. 2005;29:603-6.
20. Fariña Pérez LA, Ortiz Rey JA. Hematuria grave recidivante por amiloidosis secundaria. Mikulicz trasuretral como opción hemostática. Arch Esp Urol. 2005;58:665-8.