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Bladder Amyloidosis, Does It Present Familial Aggregation?

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Abstract

Purpose: Bladder amyloidosis is a heterogeneous disease. The AL protein is the most common bladder amyloidosis type and familial aggregation in AL-type had not been described until now.

Methods: Patients with bladder amyloidosis diagnosed at our hospital between 1990 and 2022 were included.

Results: We describe two cases of bladder amyloidosis in two women, sisters, diagnosed at 76 and 77 years of age. A transurethral bladder resection was performed and AL-type amyloidosis was diagnosed. One patient (50%) has a recurrence 28 months after the intervention. In both cases, systemic amyloidosis were ruled out.

Conclusion: It is an interesting disease for the urologist because it can simulate a bladder tumor, the diagnosis must be confirmed by bladder biopsy and systemic amyloidosis must be excluded with a complete blood count, urine proteins, renal and liver function, electrolytes and troponins.

Introduction

Amyloidosis is a heterogeneous disease characterized by a deposition of (typical) proteins and amyloid fibrils in the extracellular space. Due to this deposited material, a structural modification may occur and alter the function of one (localized amyloidosis) or several organs (systemic amyloidosis) producing multiple symptoms [1,2].

Amyloidosis classification depends on the type of fibril protein accumulated and whether it is considered a localized or a systemic disease. The AL protein (immunoglobulin light-chain amyloid) is the most common protein [1,3] and it is associated with both localized and systemic amyloidosis. Transthyretin amyloidosis (ATTR) due to transthyretin amyloid deposition, is include in the category of hereditary systemic diseases [3], as AA amyloidosis (serum amyloid A) which is usually secondary to chronic inflammatory diseases (autoimmune diseases, tumors or infections) and generally presents as a systemic disease [2,4,5].

The urinary tract is a frequent site where the fibrils are deposited, especially the kidney (because of its involvement in the systemic form). The second most affected organ is the bladder, which can be affected in both localized and systemic forms. Urethral involvement has also been described [6,7].

Localized bladder amyloidosis is AL type in 94% of cases and has better prognosis than systemic amyloidosis with a low rate of progression to that [1,8]. It occurs in the 5th-6th decade of

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life [8,9], and is more frequent in males [1,6,10]. It has been proposed that a chronic inflammatory environment increases the recruitment of lymphoplasmacytic cells in the bladder submucosa and thus leads to the production of abnormal immunoglobulins [11].

The classic clinical symptoms are very similar to those of bladder tumors, with hematuria and lower urinary tract symptoms, mainly irritative [6,8,10]. However, in more recent series, the presentation in more than 60% of cases was in the form of an asymptomatic bladder mass [9].

Diagnosis is usually made with ultrasound and cystoscopy. Areas of edema, localized lesions mimicking a solid bladder tumor or yellowish-white plaques corresponding to amyloid deposits in the bladder wall may be seen [5]. It must be confirmed by bladder biopsy, typically by transurethral resection. In the pathological specimen, deposits of acellular eosinophilic material between lamina propria and superficial muscularis propria layer are observed. Typical findings are the affinity for the Congo red dye and its increased green or apple-green birefringence under polarized light [6].

Treatment is focused on symptomatic control, with no specific treatment being necessary. Generally, the biopsy is diagnostic and therapeutic, however, in some cases more aggressive measures are necessary and in extreme cases a cystectomy may be performed [10].

Material and methods

Patients with bladder amyloidosis diagnosed at our hospital between 1990 and 2022 were included.

Results

We describe two cases of bladder amyloidosis in two women, sisters, diagnosed at 76 and 77 years of age.

In the first case the symptoms began with macroscopic hematuria. Abdominal ultrasound and CT scan showed a solid intravesical parietal lesion measuring 16x12mm and a second adjacent lesion with suspected involvement of the right ureteral meatus.

A transurethral bladder resection was performed, observing a 20x20mm mass at the bladder base with a solid and yellowish appearance. The pathological result was AL-type amyloidosis with affinity for Congo red dye.

Follow-up was carried out with cystoscopy at 3 months and annual clinical and cystoscopic control. The patient died 11 years later due to complications following a pertrochanteric hip fracture.

The second woman (the younger sister) had chronic bladder pain (with poor response to treatment) and recurrent infections, with no cytological or ultrasound findings. Treatment was started with intravesical hyaluronic acid instillations, with partial improvement of symptoms. A urodynamic study was conducted, showing only a painful sensation after 80cc of filling. Cystoscopy was poorly tolerated, but multiple glomerulations and ulcerated areas in the trigone were observed, therefore a bladder biopsy was performed by transurethral resection and hydrodistention. On the bladder wall, a positive Congo red eosinophilic deposit with green birefringence under polarized light was detected **(Figure 1a and 1b)**.

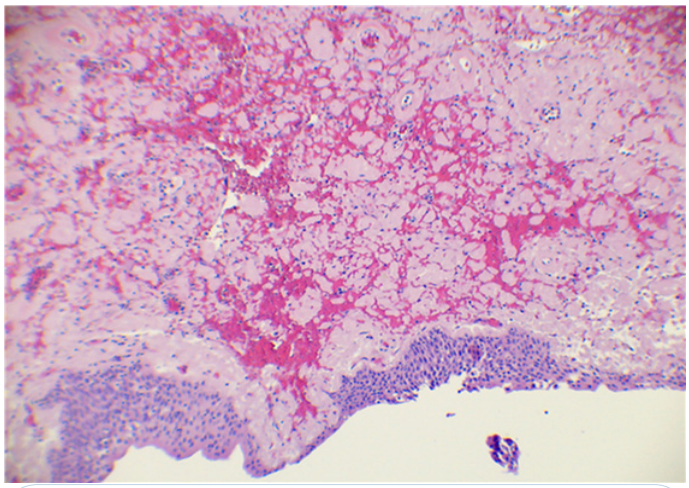

Figure 1a: Hematoxylin eosin staining, bladder wall. There is a hemorrhagic infiltration with deposition of eosinophilic material in the bladder mucosa and lamina propria.

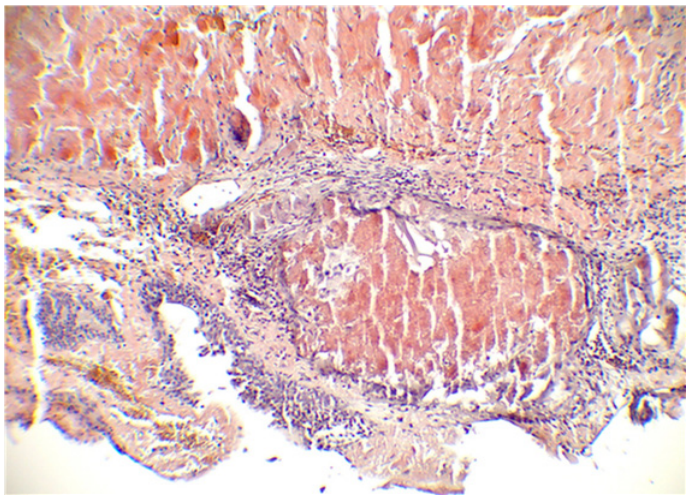

Figure 1b: Congo red staining. There are some hyaline deposits, stained Congo red. In this case, a green birefringence was observed under polarized light.

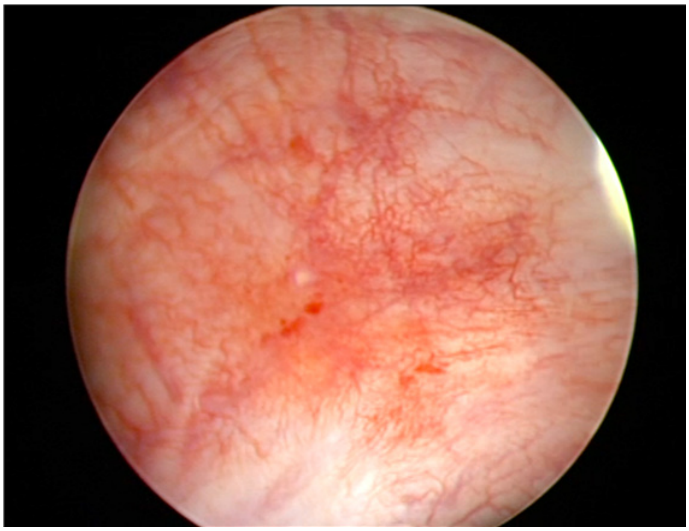

Figure 1c: Red zone on the bladder wall mucosa.

After that, the symptoms clearly improved. Clinical follow-up, ultrasound and annual cystoscopy were performed. At 28 months after the intervention, when the symptoms reappeared and new glomerulations were observed in the cystoscopy, with an erythematous lesion in the bladder fundus **(Figure 1c)**, a new hydrodistention and electrocautery of the erythematous areas was carried out with a new improvement of the irritative symptoms. The patient was followed up for 48 months with no new symptoms.

In both cases, systemic amyloidosis and the existence of other inflammatory diseases or diseases traditionally associated with amyloidosis were ruled out, so they were labeled as localized amyloidosis, AL-type.

Discussion

Bladder amyloidosis is an uncommon disease. Single cases and short clinical series ranging from 9 to 31 patients have been described in the literature [6,8-10]. The etiology of amyloidosis has been poorly studied and familial aggregation in AL-type had not been described until now (unlike amyloidosis caused by AA and ATTR proteins that can be associated with familial or hereditary forms) [3]. It is an interesting disease for the urologist because it can simulate a bladder tumor and, if diagnosed, requires multidisciplinary management to rule out systemic involvement. It manifests as macroscopic hematuria, irritative urinary symptoms or chronic pelvic pain and a bladder biopsy should be performed. Although it is rare, its diagnosis may increase in the coming years due to the growing use of diagnostic tests.

In addition to treating the local symptoms of bladder amyloidosis, it is important to exclude systemic amyloidosis. AL amyloid deposition predominates in localized forms, but it is also responsible for 38% of systemic forms, so systemic involvement cannot be excluded [1]. There is no consensus on how to carried out this screening. An initial study was performed at our center using a complete blood count, urine proteins, renal and liver function, electrolytes and troponins. Some authors recommend the addition of an abdominal fat biopsy [1] while others prefer a rectal biopsy, bone marrow biopsy or determination of serum amyloid P-component [3]. Patients with systemic amyloidosis should be treated in a referral center.

Bladder instillation with Dimethyl Sulfoxide (DMSO) has been proposed as adjuvant treatment in cases with persistence of symptoms despite surgical treatment [10,12]. However, except in cases of large bladder masses or early recurrence, these treatments are not necessary, as in the case of our patients in whom symptoms were controlled only with surgical treatment [3].

Once systemic involvement had been ruled out, clinical follow-up of symptoms was carried out, and given the recurrence of symptoms, cystoscopy and eventual transurethral resection were performed for symptom control. Several authors propose annual cystoscopies during follow-up, even in the absence of symptoms, since in some series the prevalence of urothelial tumor exceeds 50% of patients with bladder amyloidosis [3,9,13], probably due to the patient's age (60 years on average) and the role of Amyloid Precursor Protein (APP) [1] in bladder tumor oncogenesis, whose determination also correlates with size, grade and staging [14].

Despite being a benign pathology, it can affect quality of life and even compromise the patient's life in those who develop a systemic form (less than 1%) [1,8]. Patients with localized disease may require multiple interventions (as in one of our cases), with a recurrence rate as high as 35-50%, or even partial or total cystectomy, both in the short and long term [1,6,10]. The time to recurrence is variable, Pyrgidis et al. [1] estimate an average of about 20 months, but it can appear up to 168 months so it is difficult to establish the end of follow-up of patients.

Conclusions

Primary bladder amyloidosis is a rare entity but is part of the differential diagnosis of bladder tumor. The cause is unknown, but familial aggregation suggests that there may be a hereditary susceptibility also in cases of AL type amyloidosis. Systemic involvement should be ruled out and follow-up imaging or cystoscopy should be conducted periodically.

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