CASE REPORT

Difficulties in the diagnosis of primary amyloidosis: case report

Dificuldades no diagnóstico da amiloidose primária: relato de caso

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ABSTRACT

Amyloidosis consists of a group of diseases that have in common the extracellular deposition of a substance composed primarily of amyloid type proteins. Amyloid proteins have ultrastructural and biochemical specific properties that, through specific staining methods, demonstrate their fibrillar character and structure and distribution in the tissue in which they are deposited. The physical presence of deposits of an amyloid substance can cause dysfunction in tissues and organs by the interaction of fibrils with local receptors and deposit cytotoxicity. The clinical presentation varies according to the affected tissue and organ; it can be subtle and nonspecific, such as fatigue and weight loss, and serious with renal, cardiac, and gastrointestinal insufficiency and peripheral autonomic and/or sensitive-motor neuropathy. In general, though several organs may be affected, one form might dominate. Amyloidosis can be primary, hereditary, or associated with various clinical situations; being primary if it is not associated with any other disease. The secondary form of the disease occurs primarily associated with neoplasms and inflammatory or chronic infectious diseases.

Key words: Amyloidosis; Kidney Diseases; Proteinuria.

RESUMO

A amiloidose consiste em grupo de doenças que possuem em comum o depósito extracelular de substância constituída principalmente por proteínas do tipo amiloide. A proteína amiloide possui propriedades ultraestruturais e bioquímicas específicas de modo que, sob métodos específicos de coloração, é possível demonstrar seu caráter fibrilar e caracterizar sua estrutura e modo de disposição nos tecidos nos quais ela se deposita. A presença física dos depósitos de substância amiloide pode ocasionar disfunção dos tecidos e órgãos onde esteja, por interação das fibrilas com receptores locais e por citotoxicidade dos depósitos. A apresentação clínica varia conforme o órgão e tecido acometido; pode ser sutil e inespecífica, como fadiga, perda de peso, até mais grave, com insuficiência renal, cardíaca, gastrintestinal e neuropatia periférica autonômica e/ou sensitivo-motora. Em geral, embora vários órgãos possam estar acometidos, uma das formas pode predominar. A amiloidose pode ser primária, hereditária ou estar associada a várias situações clínicas; e se não estiver associada a qualquer outra enfermidade é primária. A forma secundária da doença ocorre principalmente associada às neoplasias, doenças inflamatórias ou infecciosas crônicas.

Palavras-chave: *Amiloidose; Nefropatias; Proteinúria.*

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INTRODUCTION

Amyloidosis is a rare disease, resulting from the deposit of amyloid substance – protein – in various tissues such as heart, liver, and kidneys.[1]

It can be classified in three forms: **primary**, occurring in isolation or associated with clonal lymphoid disease; **secondary**, reactive, or acquired, which most commonly occurs as a complication of chronic inflammations or infections that lead to the production of acute phase reactive proteins in the liver; and **hereditary**.[2,3] The current classification is based on the type of protein of amyloid fibrils, which are related to distinct clinical forms, with the first letter as A of amyloid, and the remaining letters referring to their biochemical or clinical nature (Table 1).

The most common form of systemic amyloidosis is the light-chain amyloidosis (AL), also called primary amyloidosis, or associated with multiple myelomas. The average age of diagnosis is at 60 years old with a male predominance of 2:1.[1]

Several theories believe that tissue damage is due to several mechanisms, however, not only fibrils deposit (its terminal medium) produces the disease but also their precursor structures that can interact with damaged cells. These structures can contain rings capable of crossing the cell membrane and damage cells.[2] Among these structures, the monoclonal population of marrow plasma cells, which produce small lambda and kappa fragments, or immunoglobulin, abnormally processed by enzymes from macrophages, can be highlighted determining the formation of partially degraded light chains responsible for primary amyloidosis.[3] The lambda class chains overlaps the kappa chains in the ratio of 2:1.[4]

The symptoms associated with amyloidosis, although some nonspecific manifestations are very frequent, such as fatigue or anorexia, generally relate to the affected organ.[2] Proteinuria, as the first sign associated with the systemic disease with renal impairment, is common. Peripheral neuropathies are most commonly associated with familial amyloidosis and dementia and cognitive impairment to brain amyloid deposits. The organs, particularly liver, kidneys, spleen, and heart, may suffer increased size in the case of primary and secondary amyloidosis, which does not occur in familial amyloidosis and amyloidosis associated the Alzheimer's disease.[4]

Kidney involvement is usually manifested by proteinuria with urinary sediment, sometimes presenting some erythrocytes. The renal lesion is generally irreversible, leading to progressive azotemia, and death. The prognosis does not seem to be related to the degree of proteinuria but improves considerably with peritoneal dialysis or hemodialysis or even renal transplant.

Hypertension is not common; however, it can occur mainly in long-term amyloidosis. There may also be renal tubular acidosis and renal vein thrombosis.[2,4,5] In about one-third of cases of systemic amyloidosis, the cardiac clinical manifestations are usually: congestive heart failure due to restrictive cardiomyopathy, cardiomegaly, systolic dysfunction, postural hypotension, and arrhythmias.[6] These manifestations reflect the existence of diffuse amyloid deposits in the myocardium. However, the endocardium, valves, and pericardium can also be affected.[4]

Table 1 - Classification of amyloidosis

	Precursor Protein	Amyloid protein	Related disease	Affected organs
Systemic forms	Light chain	AL	AL AMYLOIDOSIS	Kidney, TGI Liver, Spleen, Soft Tissues, Peripheral SN, Thyroid and Adrenal
	Serum amyloid (SAA)	AA Hereditary AA	AA FFM, TRAPS, Muckle Wells Amyloidosis	Kidney, TGI Liver, Spleen, Soft Tissues, Autonomous SN, Thyroid and Kidney
	Heavy chain	AH	Plasmocytes disease Non-myeloma	Kidneys. Heart and Nerves
	TTR, Apo AI and AII, fa, LIS, GEL, CIS	ATTR, AAAPoAI, AApoAII, AfibA, Alis, Agel, Acis	Familial amyloidosis	Variable, kidneys in ApoAI, ApoAII, Lis
	TTR (wild type)	ATTR	Senile amyloidosis	Heart and soft tissues
	B2 micro-globulin	AB2M	Amyloidosis of Dialysis	Periarticular bone tissue
Localized forms	Amylin	AIAPP	Diabetes mellitus type II and Insulinoma	Pancreas
	Calcitonin	ACal	Medullary Thyroid Carcinoma	Thyroid
	Atrial natriuretic factor	AANF	Atrial amyloidosis	Heart
	AB Protein	AB	Alzheimer's Disease Down Syndrome	Brain
	Prolactin	APro	Prolactinoma	Pituitary
	Prion Protein	AprP	Creutzfeldt-Jakob Disease Spongiform Encephalopathy	Brain

The disease progression depends on the organ involved. Cardiac involvement is generally an important determinant of poor prognosis.[7]

Gastrointestinal clinical manifestations are common in systemic amyloidosis and include obstruction, ulceration, malabsorption, hemorrhage, protein loss, and diarrhea; tongue, esophagus, and intestines infiltration may occur causing digestive bleeding.[4] The observation of nodules or asymptomatic plaques, single or multiple, pinkish-brown, involving face, periauricular, genitals, trunk, and limbs are common in cutaneous manifestations.[8]

The diagnosis of renal amyloidosis requires a renal biopsy (Figure 1) while the cardiac involvement requires a two-dimensional echocardiography, which may reveal thickening of right and left ventricle, normal left ventricular cavity, and diffuse hyper refringence of "grainy flickers" in addition to increased silhouette.[4] Systemic amyloidosis may be identified through aspirated abdominal fat or kidney, rectal, salivary glands, gums, and skin biopsies.[7] The Congo red dye, widely used and useful confers peculiar green bi-refringence when stained tissue sections are examined under a polarizing microscope.[4]

The choice of treatment depends on the type of amyloidosis. In the primary form, depending on the degree of patient risk, intravenous therapy with a high dose of melphalan may be used, with stem cell transplant, or cyclic melphalan and prednisolone orally.[4] However, there is no satisfactory therapeutic, although several schemes have been used for patients with AL amyloidosis such as: melphalan (or cyclophosphamide) + prednisone; colchicine; melphalan + prednisone + colchicine; others (VAD, D-penicillamine, vitamin E, thalidomide, alpha interferon); bone marrow transplant.[4,10,11] Among these schemes, the most used is melphalan in combination with prednisone due to results in multiple myeloma therapies. The results presented in this procedure have been proved unsatisfactory and endowed with certain inaccuracy, although it is important to note that high doses of intravenous melphalan associated with the transplantation of stem cells seem to produce good response, with remission, improvement of organ function, and thus in the quality of life.[10,11]

In nephropathy amyloidosis, response to this chemotherapy has been reported, especially in cases of nephrotic syndrome.[9,11-16] In patients with whom progress to renal failure with consequent need for hemodialysis was observed, survival is short, and their tolerance to hemodialysis is low, manifesting frequent episodes of hypotension during the sessions.

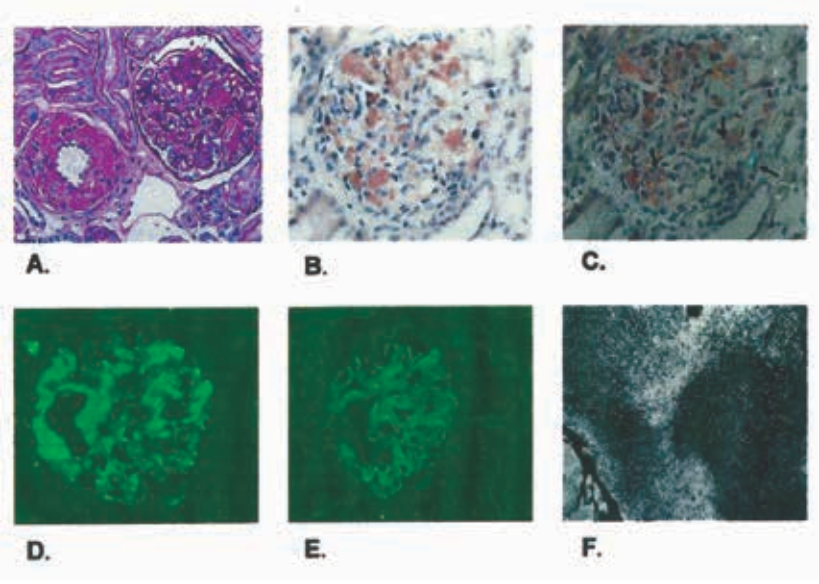

Figure 1 - Kidney biopsy in a patient with primary amyloidosis. (A) The staining with Schiff periodic-acid produces nodular appearance, which is mainly verified in the renal mesangium and vessel wall. (B) The staining with Congo red shows amyloid deposit in an orange tint, when viewed in non-polarized light. (C) When observed under polarized light, staining with Congo red produces a subtle green birefringence image. (D) Strong reactivity of light lambda chains in immunofluorescence. (E) Weak reactivity of light kappa chains in immunofluorescence. (F) fibrils with a diameter of approximately 10 nm, observed in electron microscope. Source: Dember.[9]

Also in amyloid nephropathy, renal transplants have been performed; however, in these cases, the survival of the transplanted kidney is lower than that of patients with primary renal lesions; amyloid in kidneys have been described after the transplant.[9,17] Other agents such as thalidomide, bortezomib, and lenalidomide can be highlighted as showing promising results in the treatment of systemic amyloidosis.[18,19]

CASE REPORT

A 75 years old patient, from São Paulo-SP, female, black, single, homemaker, was admitted at the State Public Servant Hospital (HSPE) for the investigation of progressive swelling of upper limbs that started three days before, which reached anasarca and dyspnea on moderate exertion. Developed nausea and vomiting, malaise, foamy urine, and decreased urine volume 24 hours later.

Previous history of osteoporosis, iron deficiency anemia, hypertension, dyslipidemia, asthma, and more recently Alzheimer's disease. Made use of quetiapine, simvastatin, paracetamol, enalapril, ferrous sulfate, and furosemide for the edema without success. She did not report pathological family history.

Presented herself on admission in good general condition, the axillary temperature of 38.2 °C; visible pale mucous membranes d+/4+, acyanotic, anicteric; eupneic, conscious, lucid, and oriented. The pulse frequency was 88 bpm, blood pressure of 140 x 80 mmHg, no murmurs on auscultation. Presented vesicular murmur, globally decreased, with reduced bronchophony, dullness to percussion-based and at the middle low third in both hemithoraces, saturating 98% with nasal oxygen catheter at 3 L/min. The abdomen was slightly diffusely painful, DB-, RHA+ and edema ++/4+ in the upper limbs and +++/4+ in the lower limbs, greater in the leg and ankle regions, symmetrical, with free calves. Presented thick lingual mucosa with whitish plaques.

In the evolution, she reported ventilatory-dependent pain and increased the intensity of dyspnea, diarrhea with some episodes of bleeding with a similar appearance to coffee grounds.

The complementary exams revealed:

- **total abdominal ultrasound:** cholecystectomy, signs of bilateral nephropathy, atheromatous aorta with preserved caliber and left pleural effusion; urinary tract with suggestive signs of bilateral kidney disease, with loss of parenchymal-sinus differentiation, without dilation of the pyelocalyceal system, with right kidney measures of: 10.1 cm and thickness of 1.8 cm, and left kidney 10.1 cm and thickness of 1.8 cm;
- **chest tomography:** moderate bilateral pleural effusion, greater on the left side, associated with compression atelectasis in the adjacent parenchyma, with no alterations in lung parenchyma, and small pericardial effusion and absence of mediastinal or perihilar lymph adenomegalies;
- **high digestive endoscopy:** mild gastritis and hiatal hernia without signs of bleeding;
- **colonoscopy:** no signs of bleeding and findings of colonic diverticular disease;
- **echocardiogram:** ejection fraction of 65%, thickened mitral, aortic and tricuspid valves, discreet pericardial effusion, PSAP 54 mmHg, mild diastolic dysfunction in the left ventricular myocardium with infiltrating aspect compatible with storage disease;
- **tongue biopsy:** no granular cell tumor;
- **bone marrow biopsy:** absence of plasmocytes in the material, free of neoplastic involvement;
- **biopsy of subcutaneous tissue:** negative for amyloid material with lipophagic granulomas;
- **myelography:** plasmocytes at the ratio of 14.5%;
- **renal biopsy:** kidney corticomedullary fragment containing six glomeruli, one of them with global sclerosis, interstitial with mild fibrosis and lymphocytic infiltrate, preserved tubules, hyaline focally wall in one of the arterioles, with positive staining specific for the Congo red technique in the examined sections.

Other exams were performed during her hospital stay (Table 3).

Table 2 - Complementary exams after hospital admission

Urea (VR:12-40mg/dL)	21	mg/dL
Creatinine (VR:0,6-1,1 mg/dL)	0.7	mg/dL
Sodium (VR:136-145 mEq/L)	142	mEq/L
Potassium (VR:3,5-5,1 mEq/L)	3.8	mEq/L
Calcium (VR:8,4-10,2 mEq/L)	7.5	mEq/L
Total protein (VR: 6,0 a 8,3 g/dL)	4	g/dL
Albumin (VR:3,4- 5,0 g/dL)	2.2	g/dL
Red series (Hb/Ht) (VR: 12-16g/dL/35-47%)	11,1/34,8	g/dL /%
VCM/HCM(VR:80-100fl/27-32pg)	90,5/29	fL/pg
White series/ Leukocyte (VR:4000-11000/mm³)	6.7	/mm³

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Table 2 - Complementary exams after hospital admission

Platelets (VR:150-450.000/mm³)	603.000	/mm3
C3/C4 (VR:90-170mg/dL/12-36mg/dL)	183/71	mg/dL
TSH/FT4 (VR:0,3-4,0 µUI/dL/0,8-2,0 ng/dL)	2.55/1.9	µUI/dL/ng/dL
Urine -I leukocytes (VR:até 10.000 cels/ml)	1000	cels/ml
Proteins (Urine I)	+++	–
Proteinuria of 24h (VR: até 30mg)	3960	mg
Hep C/B and HIV	Non-reagent	–

Note: VR (Reference value) obtained from the HSPE Laboratory.

DISCUSSION

Amyloidosis is a generic term for a heterogeneous group of associated diseases with abnormal deposition of fibrillar proteins.[20] It is classified according to the type of precursor protein that form amyloid fibrils and distribution of amyloid deposition in a localized form or systemically.[20]

The clinical manifestations of amyloidosis depend on the type of precursor protein, its tissue distribution, and amount of deposition of the amyloid substance.

Table 3 - Evolution of complementary exams during hospitalization

Exams	VR	Date							
		May/10	May/14	May/16	May/23	May/26	June/01	June /19	Aug/13
Albumin	3,4-5,0 g/dL	2,2			1,8		1,9		2,2
TGO	15-40 U/L	26					26		17
TGP	10-40 U/L	31					32		14
Calcium	8,4-10,2 mEq/L	7,8					7,5		6,9
Urea	12-40 mg/dL	21	34	53			60	29	31
Creatinine	0,6-1,1 mg/dL	0,7		0,9			2	0,8	0,9
FA	≤ 125 U/L	292					185		256
K	3,5-5m Eq/L	3,8	3,8	4,1			3,9	4,5	3,6
Na	135-145 mEq/L	142	141	145			149	142	143
P	3-4,5 mg/dL	4,2					4,7		
Hb	12-16 g/dL	11,1	10,6	10,3		9,6	8,8	8	9,6
Ht	35-47%	34,8	33,3	34,4		31,6	28,2	26,8	30,9
Leukocytes	4000-11000/mm³	6,7	6,74	21,34		14,01	9,52	5,38	4,54
Platelets	150-450.000/mm³	603000	609000	590000		714000	657000	503000	343000
C3	90-170 mg/dL	183							
C4	12-36 mg/dL	71							
TSH	0,3-4,0 µUI/dL	2,55						2,85	
T4L	0,8-2,0 ng/dL	1,9						1,6	
CT	≤ 200 mg/dL	285	238						
HDL	≤ 40 mg/dL	59	50						
LDL	≤ 160 mg/dL	207	160						
TG	≤ 150 mg/dL	93	140						
PCR	0,1-1,0 mg/dL		1,13	10,13			1,22	0,41	0,43
FAN	Não reagente		Non-reagent						
p-ANCA	Não reagente				Non-reagent				
c-ANCA	Não reagente				Non-reagent				
IgA	70-400 mg/dL					145			66,8
IgG	694-1618 mg/dL					338			361
IgM	60-263 mg/dL					57			79,8
IgE	10-179 UI/mL					38,1			
TAP	10-13s						16,1		12
INR	0,9-1,1 s						1,34		1,02
TTPA	24-45 s						29,8		24,2
B2 micro-globulin	30-330 mg/24h								3715

The most common forms of amyloidosis are systemic, primary (AL), and secondary (AA amyloidosis). The main amyloid deposition sites are clinically more significant in the heart, kidneys, and liver. In certain diseases, the clinically significant amyloid deposition can be limited to one organ.[20-22] The involvement of kidneys repeatedly presents only as asymptomatic proteinuria or nephrotic syndrome. However, the primary deposition may be confined to blood vessels or tubules with progression to renal failure with little or no proteinuria. The final-stage of the renal disease is the leading cause of death in the minority of patients.[22]

In this report, the patient presented edema and dyspnea at admission that needed clarification and nonspecific symptoms such as diarrhea and also nonspecific complementary exams. Edema and dyspnea are common characteristics to congestive heart failure. However, the echocardiogram showed few alterations that could justify the clinical manifestations. Because she presented diarrhea, colonoscopy and upper endoscopy were performed, which presented not worthy alterations.

Urinalysis I (EAS) was very important to direct the research, specifically proteinuria, which initially was important and determined the course of examinations. In an attempt to avoid invasive procedures and the risk of major complications in elderly patients, the investigation was continued with less invasive tests such as transthoracic echocardiography, colonoscopy, and endoscopy, which showed nonspecific findings. The investigation was extended to more invasive procedures such as biopsies. However, the results of such tests, such as biopsy from adipose tissue and tongue showed no particular change. Bone marrow biopsy was performed, yet without disclosing the diagnosis to justify anemia or another systemic disease. Finally, with the renal biopsy, the diagnosis of amyloidosis was established, explaining the clinical manifestations reported by the patient.

The pathological study of the renal biopsy was essential for establishing the diagnosis. The classic indications for renal biopsy are mainly the presence of nephrotic syndrome or renal involvement in the context of a systemic disease, and in patients with acute renal failure of unknown cause. Thus, after obtaining the pathological diagnosis, we could proceed to perform the necessary therapeutic interventions and simultaneous assessment of the prognosis according to the type of kidney disease affecting the patient.[21]

In another group of patients, renal biopsy could also provide important information for the diagnosis, including those that manifest themselves clinically as non-nephrotic nephropathy, proteinuria, hematuria, and chronic renal failure.[21]

CONCLUSION

Amyloidosis is a serious disease, of difficult diagnosis due to the nonspecific clinical manifestations. Many cases are undiagnosed and often only considered as amyloidosis when the patient manifests organ failure. Therefore, this case is an alert to physicians to pay more attention to this clinical entity and reiterate the importance of early diagnosis. This case consisted of primary amyloidosis, which is a rare entity, and with the involvement of kidneys as the early manifestation of the disease. It emphasizes the importance of renal biopsy as the defining element for the diagnosis, noting that, when reaching an early diagnosis, it is possible to carry out the appropriate treatment for disease stabilization, thus improving assistance and outcomes.

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