Systemic AA amyloidosis induced by benign neoplasms

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Nefrología 2008; 28 **(1)** 93-98

SUMMARY

Amyolidosis is a systemic disorder characterized by the extracelllular tissue deposition of insoluble, toxic aggregates in bundles of β-sheet fibrillar proteins. These deposits are typically identified on the bases of their apple-green birrefringence under a polarized light microscope after staining with Congo red, and by the presence of rigid, nonbranching fibrils 8 to 10 nm in diameter on electron microscopy. The type of amyloid fibril unit can be further defined by immunohistology or by immunoelectron microscopy. It has been described at least 25 different human protein precursors of amyloid fibrils, which will describe its corresponding amyloid disease. The most common types of amyloidosis are AL (primary) and AA (secondary) types; the former, is the most frequent and is due to deposition of proteins derived from immunoglobulin light chain fragments, occurring alone or in association with multiple myeloma. The later (AA), is caused by deposition of fibrils composed of fragments of the acute phase reactant serum amyloid A (SAA) and complicates chronic diseases with ongoing or recurring inflammation, namely; rheumatoid arthritis (RA), juvenile chronic polyarthritis, ankylosing spondylitis, familial periodic fever syndromes (Familial Mediterranean Fever), chronic infections and furthermore, some neoplasms (mainly renal cell carcinoma and Hodking's disease). Despite its less frequent association, some benign neoplasms can subsequently complicate to AA amyloidosis, therefore, an early diagnose and successful treatment may lead indeed, to regression of the amyloid disease. Herein, we present two cases of AA amyloidosis, both of them caused by 2 different benign neoplasms: 1. A 34 year-old woman, after chronic oral contraceptive use, developed an hepatic adenoma (fig. 1) which finally lead to AA amyloidosis with primary kidney presentation (pure nephrotic syndrome) (table 1). Post-surgical complications yield to acute renal failure from which unfortunately could not be recovered. After being on hemodialysis therapy during 10 months she received a first renal allograft without any complication. 2. A 20 year-old woman, was diagnosed of AA amyloidosis after a renal biopsy (fig. 2) because of nephrotic syndrome (table 1). Further investigation lead to the finding of a hialyne-vascular type Castleman's disease located in the retroperotoneum (fig. 2). Despite surgical resection and medical treatment (colchicine) she developed progressive renal failure requiring initialization of hemodialysis therapy. After 6 years being on hemodialysis, she received a first renal allograft which is currently functioning after one year of follow-up. Although other chronic inflamatory diseases complicate more frequently to AA amyloidosis, benign tumors have to be taken into account as a potential ethiological cause for secondary amyloidosis.

Key words: *Secondary amyloidosis (AA), oral contraceptives. Benign neoplasms. Hepatic adenoma. Castleman's disease. Nephrotic syndrome.*

RESUMEN

La amiloidosis se caracteriza por el depósito de proteínas de características ultraestructurales fibrilares, con plegamiento β en capas e insolubles, que se depositan mayoritariamente a nivel de los espacios extracelulares de órganos y tejidos. Se clasifica típicamente según la naturaleza bioquímica de la proteína fibrilar, y según su distribución en el organismo podrá ser sistémica o localizada. La amiloidosis sistémica más frecuente en la práctica clínica es la denominada AL (idiopática primaria o asociada a mieloma múltiple) cuyas fibrillas están formadas por cadenas ligeras. En cambio, la amiloidosis AA (secundaria, reactiva o adquirida) es aquella que se desarrolla típicamente como complicación de una enfermedad inflamatoria crónica, destacando entre las más habituales; enfermedades de origen reumatológico (artritis reumatoide, espondilitis anquilopoyética, artritis psoriásica), la fiebre mediterránea familiar, la enfermedad inflamatoria intestinal, así como infecciones cronificadas (tuberculosis, osteomielitis). No obstante, otras causas responsables de su desarrollo y en muchas ocasiones infravaloradas, son las tumoraciones benignas. Algunas de estas entidades, también tendrán capacidad de actuar como estímulo responsable de la formación de estas proteínas, que finalmente se depositarán en diferentes tejidos del organismo. Es importante resaltar, que el diagnóstico precoz así como el tratamiento eficaz de la enfermedad subyacente ha permitido disminuir su incidencia, así como en algunos casos incluso revertirla. Aquí, presentamos dos casos clínicos paradigmáticos de tumoraciones benignas, adenoma hepático y Enfermedad de Castlemann, que desarrollaron posteriormente amiloidosis AA con afectación renal principalmente en forma de síndrome Nefrótico.

Palabras clave: Amiloidosis secundaria (AA). Anticonceptivos orales. Tumoraciones benignas. Adenoma hepático. Enfermedad de Castlemann. Síndrome nefrótico.

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INTRODUCTION

Amyloidosis is a condition characterized by predominantly extracellular deposits of a protein material, with a molecular beta tertiary structure that accounts for the insolubility and the resistance to proteolytic digestion. The classification of the disorder is made according to the type of fibrillar protein.

In secondary amyloidosis the deposits are typically constituted by a fibrillar protein AA with a non-immunoglobulin structure. The origin of this protein (SAA) is a plasmatic precursor, which is synthesized in the liver as an acute phase reactant in the presence of persistent inflammation or of tissue necrosis. Several forms of SAA proteins have been identified.[1] Systemic amyloidosis AA can be a complication of many diseases or chronic disorders. It is especially frequent in Mediterranean familiar fever, rheumatoid arthritis,[2] juvenile idiopathic arthritis,[3] ankylosing spondylarthritis,[4-6] inflammatory bowel disease, osteomyelitis and chronic respiratory infection with underlying bronchiectasis. Other conditions can also be associated to amyloidosis AA, like malignant neoplasm, such as renal cancer or Hodgkin disease.[7,8] The association to benign proliferations has only sporadically been reported.[8,9]

We present two cases to show the association between benign proliferations and the development of secondary amyloidosis (AA).

CASE REPORT (1): AMYLOIDOSIS ASSOCIATED TO HEPATIC ADENOMA AFTER TREATMENT WITH ORAL CONTRACEPTIVE

A 34 year-old patient with unremarkable family and personal history was on oral contraceptives from 1989 to 1996. In 1999 she was pregnant and delivered a child without known complications. In 2000 she took contraceptives once again. She was again pregnant in 2001 and everything went out without complications. After delivery, she reinitiated again the treatment with contraceptives. In 2002 hyperlipidemia was detected and she began simvastatine. In May of 2003 she complained about progressive morning ankle and palpebral edema, and she went to the Emergency Room. The laboratory parameters were compatible with nephrotic syndrome, together with a biochemical profile of cholestasis (table I).

The image investigations (ultrasonography and abdominal CT scan) showed a large lesion that appeared to be a hepatic adenoma in the right hepatic lobe (fig. 1a). The kidneys were normal in size and structure. A rectal biopsy was performed that revealed the existence of type AA amyloid deposits within the submucosal vessels (immunohistochemistry technique).

The diagnosis was nephrotic syndrome secondary to amyloidosis in a patient with probable hepatic adenoma. The patient was referred to the Surgery Department for elective surgery. In July of 2003 a partial right hepatectomy was performed (fig. 1b). The diagnosis of hepatic adenoma was confirmed and type AA amyloid deposits were further observed within the kidney, liver and tumor samples (fig. 1c, d).

The evolution after the surgery was torpid. A high volume ascites appeared and the renal function deteriorated progressively. A septic shock with E. Coli of peritoneal origin complicated the clinical course and vasoactive drugs together with continuous renal replacement therapies were required. Once the patient got over from the acute phase and after being for several days in the intensive care unit, the evolution was favorable, except for renal function that was not recovered, and the patient was scheduled for periodic hemodialysis program. Ten months after, the patient received a kidney transplant, and the evolution to date was good (serum creatinine: 120 µmol/L, plasma albumin: 35 g/L, proteinuria: 0.5 g/day).

Table I.

	Patient 1	Patient 2
Creatinine (µmol/L)	74	85
Proteins (g/L)	4.2	4.6
Albumin (g/L)	2.2	1.5
Cholesterol (mmol/L)	12	6.7
Proteinuria (g/day)	17	6
Urinary sediment	N	N
AST, ALT (µkat/L)	0.3/0.2	0.2/0.3
GGT (µkat/L)	1.96	N
AP (µkat/L)	N	N
Bilirubin (mmol/L)	6	N
Hemoglobin (g/dL)	12	9.9
PT, aPTT, Fibrinogen	N	N
ESR (mm/h)	123	90
IgG, IgM, IgA (g/L)	13, 2, 2	10, 1.5, 2.5
Protein electrophoresis	N	N
ANA, anti-DNA, ANCA, antiGBM	Negative	Negative
Complement fractions	N	N
HBV, HIV and HCV	Negative	Negative

N: Within the normal range.
Normal ranges: Creatinine (< 86), Protein (> 65), Albumin (> 38), Cholesterol (< 5), Proteinuria (< 0.03), GGT (< 0.5), AST/ALT (< 0.5), Bilirubin (< 3), Hemoglobin (> 14), ESR (< 10), IgG (7-14), IgM (0.4-2.49), IgA (0.7-3.7).

DISCUSSION OF CASE REPORT 1

The association between hepatic adenoma and chronic use of contraceptives was first described in 1973.[10] Since then it has been increasingly reported, probably because of the increasing use of contraceptives. The incidence among women who have never taken contraceptives is approximately 1 per million population (pmp), whereas among women who are chronically treated with this drug is 30-40 pmp. Young age, high content in estrogens, and doses and duration of the treatment have been reported as possible risk factors.[11,12] The hepatic adenomas that appear in relation to contraceptives are frequently multiple, of a greater size and with higher tendency to bleeding than primary adenomas.[13-16] In some cases withdrawal of the treatment was accompanied with a regression of the adenomas, which recurred in case of pregnancy or if the treatment was reintroduced, that is to say during hyper-estrogenic states.[17-20] The pathophysiologic mechanism underlying the development of hepatic adenomas while on estrogenic therapy is not clear, although the most plausible hypothesis is hepatocytes transformation and proliferation through steroid receptors present on these cells.[21] The risk for malignization is not universally accepted, although some authors have found that it is probably not exceptional.[22] The management of the

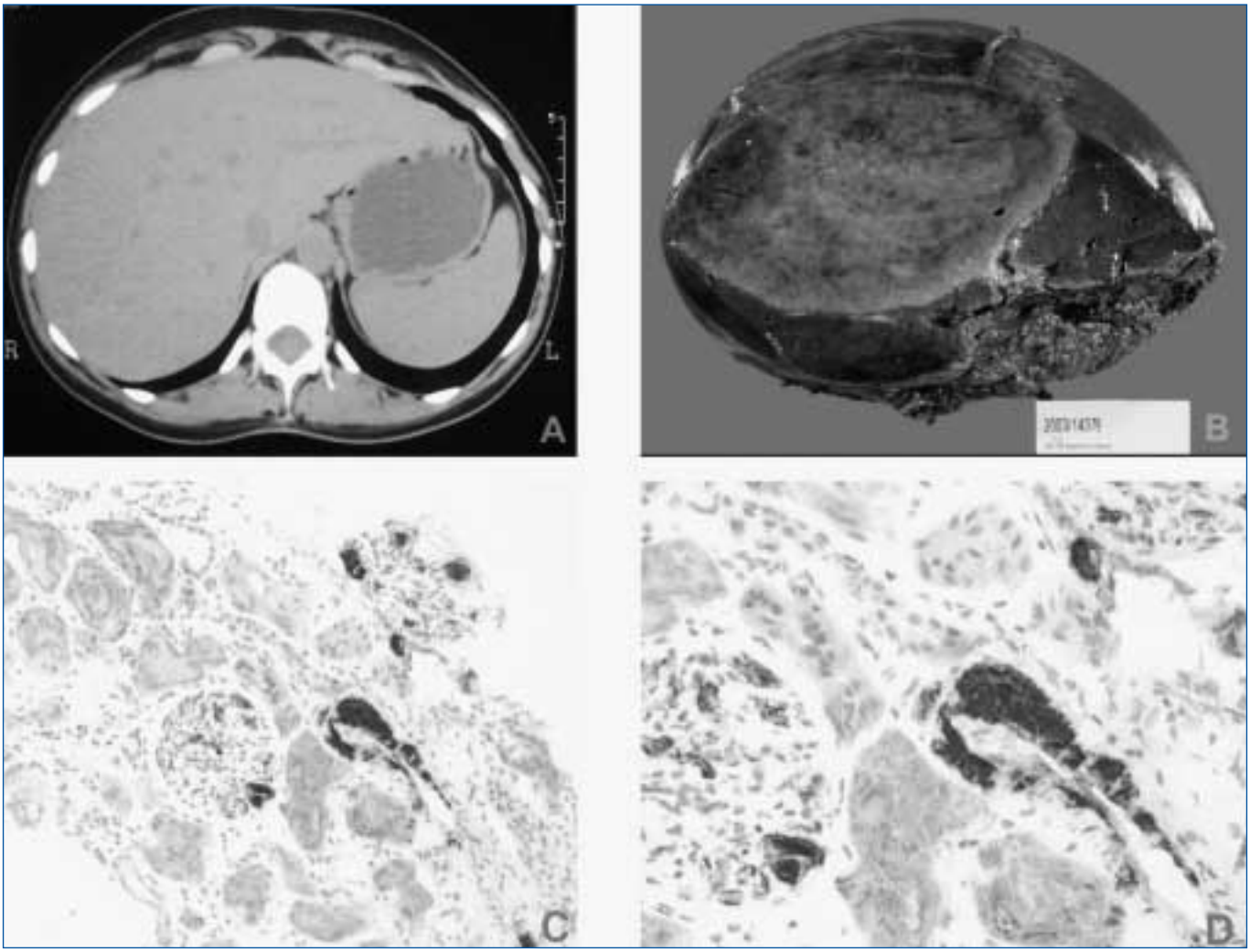

Figure 1. A) Cross-section with Computerized Tomography (CT) scan showing a large image compatible with liver adenoma at the right liver lobule. B) Surgical specimen from partial right hepatectomy macroscopically showing the liver adenoma. C) By immunohistochemical staining for amyloid protein A, type AA amyloid deposition is observed at the glomerular mesangium and the renal interstitium. D) The same image at a higher power (x400).

adenomas remains controversial. Asymptomatic patients who chronically take contraceptives and have small hepatic lesions (< 5 cm) should discontinue the treatment and are to be observed, as complete regression of the lesions after drug withdrawal has been documented.[23-25] Other authors propose surgical resection, independently of tumor size, because of the risk for tumor growth, malignization or rupture.[26] Surgical resection is the first choice therapy in asymptomatic patients with adenomas larger than 5 cm.

We found very few reports in the literature on the association between hepatic adenomas and development of secondary systemic amyloidosis (AA). It was described that the appearance of secondary amyloidosis (AA) is due to hyperproduction of TNF-α by tumoral cells, which can stimulate the production of amyloid substance.[27] Some cases of deposits regression after the surgical removal of the tumor have been reported.[28] For this reason, surgical resection was indicated in this case despite the risk of intervention in a patient with systemic amyloidosis. Tumor removal was not accompanied by improvement in renal insufficiency, probably because of postoperative hemodynamic complications. To date, 30 months after the intervention, the patient has received a kidney transplant and maintains an excellent renal function.

CASE REPORT (2): CASTLEMAN'S DISEASE AND SECONDARY AMYLOIDOSIS

A 20 year-old female, with unremarkable personal and pathological history was admitted to our Department because of asthenia and ankle edema for one month. The remaining physical examination was normal. The laboratory findings were compatible with pure nephrotic syndrome (table I). Immunological and serological examinations yielded no abnormalities. An ultrasound-guided kidney biopsy was performed that showed extended deposits of type AA proteinic amyloid material (immunohistochemistry technique) (fig. 2). With the diagnosis of secondary renal amyloidosis (AA) the etiological study was undertaken. The bone biopsy aspirate was normal. The abdo-

minal CT disclosed a retroperitoneal mass 6 x 5 x 6 cm adjacent to the inferior vena cava together with several retroperitoneal lymphadenopathies. The mass was excised by laparoscopy. The pathological examination revealed a lymphadenopathic structure with nodular proliferation of dendritic cells and hyaline appearance, typical of Castleman´s disease (CD), as well as deposits of type AA amyloid material. Nephrotic syndrome remained despite the surgical removal of the lymphadenopathic mass. Colchicine was initiated together with symptomatic medical treatment with no response, and the clinical picture evolved to chronic end-stage renal failure, which 9 months after required replacement treatment. Six years later, the patient received a kidney transplant from a cadaver donor and the course has been good to date (serum creatinine: 110 µmol/L, plasma albumin: 37 g/L, proteinuria: 0.2 g/day).

DISCUSSION OF CASE 2

Giant lymph node hyperplasia or Castleman's disease (CD) is a heterogeneous clinicopathological entity included in the group of atypical lymphoproliferative diseases. Castleman et al. described the disease for the first time in 1956 as a big lymphadenopathic mass, localized in the mediastinum and with a benign behavior. Other studies have demonstrated that the disease can also localize outside the mediastinum.[29] The classical pathological patterns of CD are vascular hyaline in 80%-90% of the cases, and the plasma cell type, in 10%-20%. The vascular hyaline variant originates from capillary proliferation inside the germinal center of the lymph follicles. It has a hyaline appearance, with only one, frequently mediastinal localization, and a benign course after its removal. The less frequent plasma cell variant is characterized by follicular hyperplasia with plasma cells, often multicentric, and can present as a clinical picture resembling a systemic inflammatory syndrome. The prognosis is worse than that of vascular hyaline type, and progression to lymphoma is not an exception. The multicentric form is frequently associated to HIV infection, as well as infection or co-infection by HHV 8.[30] Antiviral therapy can be useful to achieve disease regression.[31] Some mixed forms have also been described.

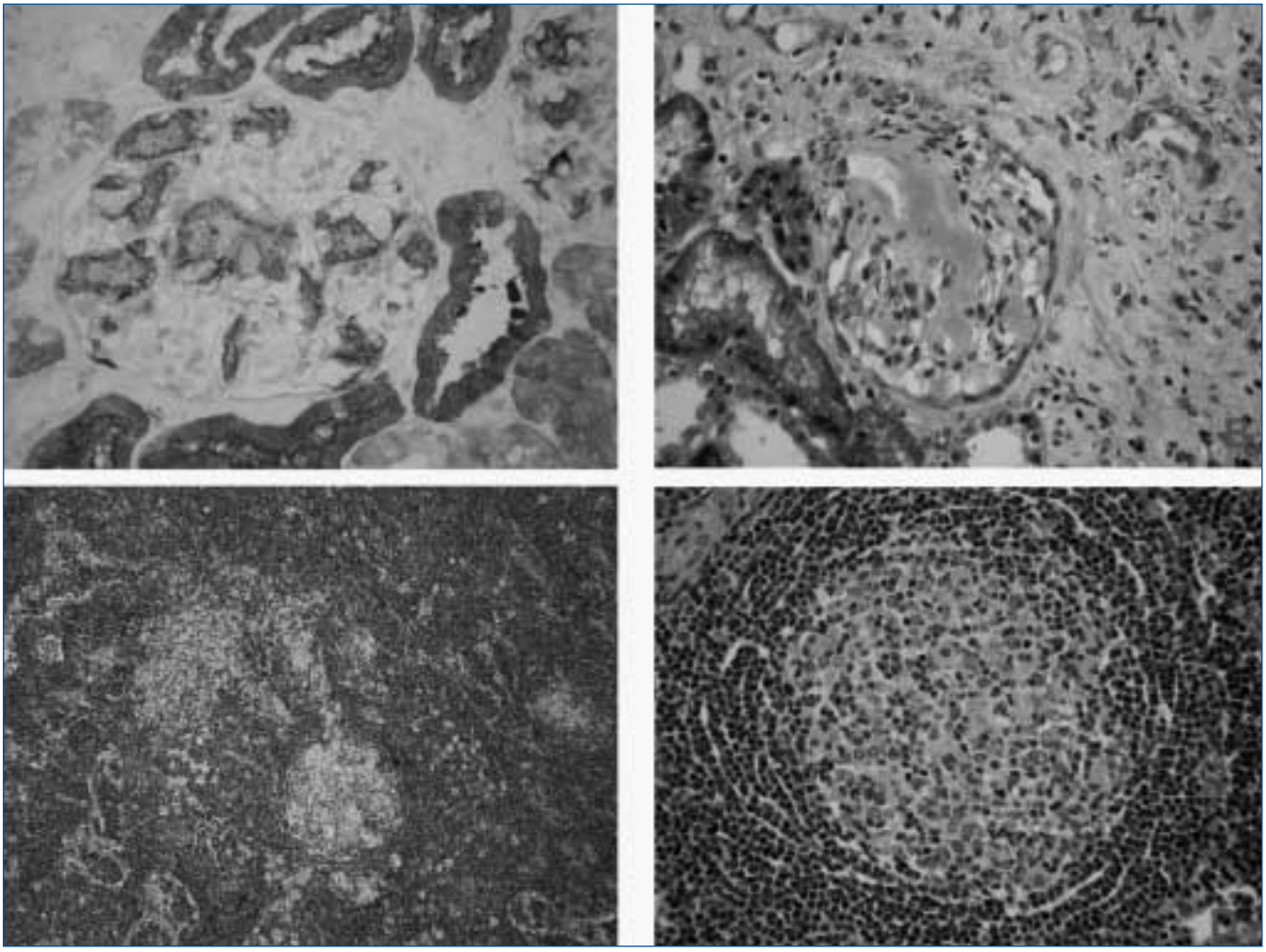

Figure 2. A) Immunohistochemical staining for amyloid protein A showing deposition at the glomerular mesangium. B) A glomerulus with mesangial deposition of amorphous acellular material. C) Interfollicular zone at high magnification (x400) showing the expansion of the mantle zone with small-sized lymphocytes concentrically arranged.

Few cases of Castleman's disease associated to amyloidosis have been reported in the literature. Only 9 out of 17 cases presented with nephrotic syndrome secondary to renal amyloidosis.[32] Other renal conditions have also been described in CD: minimal changes nephropathy, membranous and membranoproliferative nephropathy.[33] The pathogenesis of the amyloidosis AA associated to CD is not clear. Some authors have pointed out cytokine IL-6, present in great amounts inside the germinal centers of the lymph nodes, as a possible factor responsible for the release of acute phase reactants that promote the formation of amyloid deposits (PCR, SAA).[34,35] Some authors have shown that lymphoid mass resection leads to CD healing, and consequently to amyloid deposits regression with disappearance of the associated nephrotic syndrome.[36,37] However, others have showed that the amyloid deposits persist after surgery.[38,39]

In the present case it is possible that the amount of amyloid material in the kidneys was too big to disappear, even after the elimination of the causative stimulus.

CONSIDERATIONS

It is well known that the presence of type AA amyloid in a tissue sample obliges to discard a possible underlying chronic inflammatory disease as the cause of the deposit. The two reported cases illustrate that benign proliferations are also to be taken into account together with other more frequent conditions as the possible cause of secondary amyloidosis. It is important to note that early recognition of these entities can lead to healing of secondary amyloid disease, and therefore to avoidance of the multiorgan parenchymal injury that can be a feature of the disease. In the two cases, the amyloid insult to the kidney, which presented as nephrotic syndrome, did not regress despite the elimination of the causative stimulus. The first patient presented severe complications after the surgical procedure with hemodynamic collapse, which probably prevented the potential renal function recovery. The second patient had such extensive deposits of amyloid material in all renal compartments, mainly within the glomeruli and the vessels, that their elimination was impossible despite the disappearance of the primary stimulus. However, the favorable clinical renal and extrarenal evolution for both patients two years receiving a kidney transplant point out that systemic amyloid disease is resolved.

Amyloidosis AA is a systemic disease and cardiac injury has a special relevance regarding the vital prognosis as well as the possible indication for kidney transplantation. In the formerly commented cases, ultrasonic myocardial assessment revealed no functional abnormalities, both at diagnosis and before the transplantation, and it was assumed that there was no cardiac affectation. It can be concluded that once the causative stimulus for the amyloid disease disappears, renal transplantation is indicated with excellent clinical outcome.

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