Renal involvement in benign monoclonal gammopathies: an underdiagnosed condition?

R. Ramos[1], R. Poveda[1], C. Bernís[2], J. Ara[3], M. Sunyer[4], P. Arrizabalaga[5] and J. M. Grinyó[1]

[1]Nefrología. Ciutat Sanitària i Universitària de Bellvige. L'Hospitalet del Llobregat. [2]Nefrología. Hospital de La Princesa. Madrid. [3]Nefrología. Hospital Germans Trías i Pujol. Badalona. [4]Nefrología. Hospital Virgen del Rocío. Sevilla. [5]Nefrología. Hospital Clínic i Provincial. Barcelona.

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SUMMARY

Renal involvement is observed frequently in association with malignant gammopathies, mainly those related to light chain deposition, although has also been described in non-malignant monoclonal gammopathy. This study reports the clinicopathological findings and outcome in 9 patients with nephropaty secondary to monoclonal immunoglobulin deposit in absence of malignancy. They were three men and six women and they were 59.2 ± 12 years old. All patients presented proteinuria and different levels of renal insufficiency (mean creatinin = 315 ± 187 micromol/L) at the moment of diagnostic. Two patients required dialysis at the time of renal biopsy. The pathology studies revealed a nodular sclerosing glomerulopathy in four cases, mesangiocapilary glomerulonephritis in three cases, only tubular lesions in one and mesangial lesions in the other one. The treatment applied was: Prednisone alone (two cases), with chemotherapy associated (melfalan in two, clorambucil in one and ciclophosphamide in another one). One patient received plasmapheresis and mycophenolate and another patient undergone a bone marrow authotransplant associated to mycophenolate and prednisone. One of the two patients who required dialysis at the moment of presentation was not treated. After a follow-up of more than 4 years (4.89 ± DE: 3.69) renal function improved or remained stable in three patients and proteinuria was dissapaired in more than 50% of patients. Four patients had a worsening of renal function and they required dialysis during the time of follow-up (in 2.4 years ± DE: 4.3). In any case malignitation was observed. Chemotherapy stabilized or improved renal function in 3 of nine patients (33%) with non-malignant monoclonal gammopathy Non-malignant monoclonal gammopathy could go unnoticed. Appearance of abnormalities in renal routine tests deserves more in-depth diagnostic procedures, including renal biopsy. Evolution to end stage renal disease could probably be avoided or reduced in severity with early detection and treatment of this entity.

Key words: *Monoclonal gammopathy. Light chair. MGUS.*

RESUMEN

La nefropatía de las gammapatías monoclonales es debida principalmente al depósito de cadenas ligeras. Aunque se presenta sobre todo en cuadros malignos, también se ha descrito en pacientes cuya gammapatía es considerada «benigna». Se describen las características clínicas e histológicas de 9 casos de nefropatía por depósitos de cadenas ligeras diagnosticadas en el contexto de una gammapatía monoclonal sin datos de malignidad. Tres hombres y seis mujeres con edad media de 59,2 ± 12. Todos los pacientes presentaban al diagnóstico proteinuria y grados variables de insuficiencia renal con creatinina sérica media de 315 ± 187. Dos requirieron diálisis desde el inicio. La histología renal mostró patrón nodular en 4 casos, mesangiocapilar en 3, lesiones sólo tubulares en 1 y mesangial en otro. Los depósitos renales más frecuentes fueron los constituidos por cadenas kappa (67%). Los tratamientos aplicados fueron: Prednisona en monoterapia (tres casos) o asociada a quimioterapia (melfalan, clorambucil o ciclofosfamid). En dos casos se añadieron recambios plasmáticos o autotrasplante de médula ósea, respectivamente. Tras un seguimiento medio de 4,89 ± DE: 3,69 años observamos desaparición de la proteinuria en más del 50% de los pacientes y estabilización o mejoría de la función renal en 3. Dos de ellos necesitaron terapia renal substitutiva desde el inicio y existió progresión del fallo renal hasta los requerimientos dialíticos en los cuatro restantes. En caso de gammapatía monoclonal, incluso de carácter benigno, debe buscarse una posible afectación renal. La comprobación del depósito renal de cadenas ligeras debe hacer plantearse un tratamiento precoz, ya que la evolución a la insuficiencia renal terminal es frecuente.

Palabras clave: Gammapatía monoclonal. Cadenas ligeras. MGUS.

Correspondence: *Rosa Ramos Sánchez*
Ciutat Sanitària i Universitaria de Bellvitge
Feixa Llarga, s/n
08907 L'Hospitalet del Llobregat. Barcelona. España
30965rrs@comb.es

INTRODUCTION

Monoclonal gammopathies are a group of diseases characterized by abnormal production of immunoglobulins derived from a same clone of plasma cells. Whole immunoglobulins or any of their components (heavy chains, light chains or both) may be deposited in any tissue. Classification of gammopathies may be seen in table I.

Renal involvement is frequently associated to malignant monoclonal gammopathies, mostly associated to light chain deposits.[1] Traditionally, it has been seen associated to diseases such as myeloma or Waldenström macroglobulinemia.[2-4] However, renal light chain deposition has also been reported in benign monoclonal gammopathies.[5-11] There are non-malig-

Table I. Classification of monoclonal gammopathies according to The International Myeloma Working Group 2003. *Br J Haematol* 2003; 121: 749-757

- Monoclonal gammopathies of undetermined significance (MGUS).
- Multiple myeloma
  - Asymptomatic myeloma (smouldering multiple myeloma).
  - Symptomatic multiple myeloma.
  - Non-secreting myeloma.
  - Solitary bone plasmacytoma.
  - Multiple solitary plasmacytoma.
  - Plasma cell leukemia.
- Waldenström macroglobulinemia.
- Heavy chain deposition diseases.
- Primary amyloidosis.

nant conditions in which circulating paraproteins, either light chains, heavy chains or both, may show affinity for the kidney, become deposited in it, and cause renal clinical signs such as nephrotic syndrome, isolated proteinuria, or rapid, progressive renal failure.[12] Tubulopathy occurring as Fanconi syndrome has also been frequently reported.[13] By contrast, malignization of these conditions during follow-up is uncommon.[7]

A retrospective series comprising patients with renal disease secondary to paraprotein deposition in the setting of «benign» monoclonal gammopathy is reported. Their clinical, histopathological, and evolutionary characteristics are analyzed.

PATIENTS

Patients from five Spanish nephrology departments were enrolled based on the following criteria:

1. Presence of a monoclonal gammopathy with no malignancy criteria, i.e. with less than 10% plasma cells in the bone marrow sample and no extrarenal clinical findings suggesting malignant monoclonal gammopathy, such as anemia, bone lesions, or visceral involvement.
2. Clinical evidence of renal disease.
3. Availability of a renal biopsy showing paraprotein deposits.
4. Finally, detection of a monoclonal component in blood and/or urine was not considered a requirement for diagnosis, but supported it.

METHODS

Both laboratory and pathology results were evaluated by the source hospital. The monoclonal component was investigated, either in blood or urine, using electrophoresis and subsequent gel immunofixation. Renal histological study was performed using standard techniques for light microscopy and immunofluorescence. For the latter, antisera directed against alpha, gamma, and mu heavy chains, as well as against lambda and kappa light chains were used. Samples were also stained with Congo red and viewed under polarized light. Presence in deposits of a single type of light chain or amyloid substance with immunopathological characteristics of the AL type was considered to suggest monoclonality.

Treatment and subsequent follow-up were performed according to the standard procedures or experience of each center.

RESULTS

Clinical cases

A total of nine patients, three males (33%) and six females (67%) with a mean age of 59.2 ± 12 years, were included in the study.

At diagnosis, all patients had microhematuria, proteinuria, and some degree of renal failure. Proteinuria was in the nephrotic range (4 ± 1.5 g/day) in seven patients, four of whom eventually experienced a nephrotic syndrome. Mean creatinine levels at diagnosis were 315 ± 187 micromol/L, and dialysis was required from the start in two patients (table II).

In no case was the proportion of plasma cells in bone marrow greater than 10%. Laboratory findings showed different presentation forms in both blood and urine immunoelectrophoresis (table III).

Histological presentation forms were diverse. Nodular and mesangiocapillary glomerulopathy were found in four and three patients respectively, while tubular lesions alone were seen in one, and a mesangial pattern in the remaining patient (table III). Amyloidosis was not found in any patient at the time of diagnosis.

All nine patients were treated according to the standard procedure and experience at each unit. Only 7 patients were administered regular treatment, because one of the two patients with end-stage renal disease did not receive specific treatment, while the other was treated for only one month (see table II). The untreated patient (patient 6) had end-stage renal disease that required dialysis form the start. In the remaining patients, treatment regimens lasted from four to eight months and consisted of: prednisone (PDN) monotherapy in two patients, PDN plus melphalan in two patients, and PDN plus melphalan plus plasmapheresis, PDN plus melphalan plus bone marrow autotransplantation, and PDN plus cyclophosphamide each in one patient.

Follow-up time ranged from one to 12 years (4.89 ± SD 3.69). Six of the nine patients progressed to chronic renal failure and required regular hemodialysis within 2.4 years ± SD 4.3. Renal function stabilized in three cases, and proteinuria disappeared after treatment in more than 50% of patients. No patient progressed to malignancy during the follow-up period.

DISCUSSION

Our study reports a series of nine patients with benign monoclonal gammopathy and renal involvement secondary to light chain (LC) deposition.

Monoclonal gammopathies, while caused by an abnormal proliferation of plasma cells, do not always result from a malignant process either at the time of diagnosis or in a subse-

Table II. Clinical course of patients

	HYPERTENSION (> 140/90)	SERUM CHOLESTEROL (mmol/L)	MICROHEMATURIA	CREATININE PRE (µmol/L)	ALBUMINEMIA (g/L)	PROTEINURIA PRE (g/day)	TREATMENT	TREAT TIME (months)	PROTEINURIA POST-T t (g/day)	CREATININE POST- Tt (µmol/L)	PARAPROTEINEMIA POST Tt	YEARS OF FOLLOW-UP	CREATININE LAST CONTROL (µmol/L)
CASE 1	YES	7.8	YES	158	45	5.1	PDN/MELPHALAN	4	3	150	Negative	8	215
CASE 2	NO	9	YES	250	24	7	PDN/MELPHALAN	6	6	500	SC	2	PHD
CASE 3	YES	8.51	YES	246	33	3	PDN	4	0.15	225	SC	3	218
CASE 4	YES	-	YES	252	38	4.5	PDN/MMF/PLASMAPHERESIS	8	Negative	110	Negative	8	130
CASE 5	YES	-	YES	150	31	3	PDN/CHLORAMBUCIL	8	1.7	600	Negative	12	PHD
CASE 6	YES	-	YES	750	37	4	-	-	-	-	-	3	PHD
CASE 7	NO	8	YES	450	28	4.6	PDN	4	4.6	-	NC	2	PHD
CASE 8	YES	6.83	YES	79	36	4.1	AUTOTRASPLANTATION/ MF/PDN	-	5	84	-	8	PHD
CASE 9	YES	5.18	YES	681	38	1.4	PDN /CICLOPHOSPHAMIDE	1	-	875	-	3	PHD

PDN = prednisone; MMF = mycophenolate; PHDP = periodic hemodialysis; NC = No change.

quent stage. In 2003, the International Myeloma Working Group[14] classified the different monoclonal gammopathies using simple criteria easy to apply in daily clinical practice. The less clinically aggressive stage corresponds to monoclonal gammopathy of undetermined significance (MGUS), in which the circulating paraprotein, usually found at levels under 3 g/dL, is detected in the absence of significant proliferation (< 10%) of abnormal plasma cells in the bone marrow sample and clinical signs attributable to the hematological process.[15-16] If the MGUS label is considered to correspond to cases with no clinical signs attributable to paraprotein deposition, the patients reported here, who had no malignant disease but showed renal involvement secondary to LC deposition, should be excluded from the diagnostic group of MGUS and considered to have renal disease from light chain deposition.

The probability of a malignant transformation reported in different series ranges from more than 17% at 10 years of follow-up and up to 39% at 25 years of follow-up.[9,17] Our study reports a series of nine patients with benign monoclonal gammopathy and renal involvement due to immunoglobulin deposition diagnosed by biopsy in whom no malignization occurred, though the follow-up period was shorter (4.89 years ± SD 3.69).

The reason for renal involvement by monoclonal paraproteins is multifactorial and has not been fully elucidated yet.[18] While it is more commonly reported in the setting of already established malignant diseases such as myeloma or Waldenström disease,[1] renal involvement by LC deposition in gammopathies without hematological criteria of malignancy is not rare and has been reported in anecdotal cases,[5,7,8,11] short series, or in larger cohorts also including malignant cases.[10,19] Its systemic nature or its association to neuropathy or liver disease have sometimes been reported.[20,21] Monoclonal immunoglobulin deposition diseases (MIDD) show a wide variety of glomerular and/or tubular clinical presentations, and also different pathological characteristics.[22] Histological findings differentiate three forms depending on the characteristics of the paraprotein deposited:

1. Light chains with immunofluorescence positive for kappa or lambda and an ultrastructure in the form of disorganized granular deposits. This would correspond to the light chain deposition disease (LCDD) initially described by Randall.[23] These may coexist with deposition of whole immunoglobulins or heavy chains (LHCDD), or heavy chains may only be detected (HCDD).
2. Light chains with positive immunofluorescence, usually associated to IgG and C3 and with an ultrastructure of organized microtubules. Controversy exists about whether two differentiated clinical and histological subforms (fibrillary and immunotactoid glomerulopathy) exist or they are the same disease.[24]
3. Light chain deposit positive to Congo red staining: this corresponds to amyloid AL. It is common in the setting of myeloma or with the clinical picture characteristic of primary amyloidosis. Ultrastructurally, they are organized as fibrils. This variety may coexist with types 1 and 2, but association is uncommon.[25]

The typical renal presentation of MIDD includes proteinuria, hypertension, and renal failure. Renal failure was found in 88% of our patients, in agreement with other series where

Table III. Bllod and urine immunoelectrophoresis. Renal histology (NA = not available)

	Monoclonal band serum	Monoclonal band urine	Renal histology	Renal deposit paraproteinemia
CASE 1	IgA/LAMBDA	ALPHA/LAMBDA	Mesangial proliferative	Lambda light chains
CASE 2	IgG/LAMBDA	LAMBDA	Membranoproliferative glomerulonephritis	Lambda light chains
CASE 3	IgM/KAPPA	NA	Nodular glomerulosclerosis	Kappa light chains
CASE 4	No band	No band	Nodular glomerulosclerosis	Kappa light chains
CASE 5	IgM/KAPPA	MU/KAPPA	Membranoproliferative glomerulonephritis	Kappa light chains
CASE 6	KAPPA	KAPPA	Kappa deposit in tubular cells	Kappa light chains
CASE 7	No band	KAPPA	Nodular glomerulosclerosis	Kappa light chains
CASE 8	IgG/KAPPA	KAPPA	Amyloidosis at 8 years of diagnosis	Kappa light chains
CASE 9	IgA/KAPPA	KAPPA	Membranoproliferative glomerulonephritis	Kappa light chains

renal failure was reported to occur in 92%-96% of patients with pure MIDD.[6,10,26,27] However, almost 90% of our patients initially had proteinuria in the nephrotic range, as compared to only 48%-57% in other literature reports.

Kappa chains are the light chains predominately deposited in the renal basal membrane, and are identified in 73%-90% of cases.[6,10,26] In our series, a similar proportion was found (77%).

While the typical histological presentation is nodular glomerulosclerosis,[1] there may be other presentation forms that should not deviate us from diagnosis. Only four of our nine patients showed nodular glomerulosclerosis in renal histology.

Age at diagnosis was similar in our patients to that reported by other authors, approximately the sixth decade of life.[10,28]

Treatment administered in idiopathic MIDD is usually similar to that given in cases of malignant disease: prednisone/melphalan (the most common) or prednisone/chlorambucil or prednisone/melphalan plus plasma exchange or bone marrow autotransplantation.[8] These treatments have been reported to be effective for both idiopathic forms and malignant conditions. Although disappearance of the light chain deposit following chemotherapy has occasionally been reported,[1,29] in the largest series stabilization or improvement only occurred in 62%-65% of patients with serum creatinine levels under 350 micromol/L at treatment start, and 82% of patients with higher creatinine values progressed to end-stage renal disease despite treatment.[10,27] The initial degree of renal failure, age, underlying hematological disease, or extrarenal paraprotein deposition have also been reported to be prognostic factors.[19] Most our patients received steroids, whether or not associated to melphalan. Progression of renal disease was stopped in two patients, and in the patient also treated with plasmapheresis, renal function even improved and stabilized at 8 years of follow-up. The lack of renal function improvement in all other patients was attributed to the advanced degree of renal failure. Three of those patients had baseline creatinine levels higher than 350 micromol/L.

As regards proteinuria, values decreased by up to 33% after treatment in the Heilman series. By contrast, proteinuria decreased in more than 50% of our patients. Renal disease prognosis is poor according to Heilman,[10] with a five-year survival rate of approximately 37%. Our series showed a similar renal survival of approximately 33%. Unfortunately, no conclusions may be drawn about efficacy with the different treatment regimens because of the small number of patients, the lack of treatment standardization, and the limited follow-up time.

CONCLUSION

Monoclonal gammopathies, while «benign», may be associated with renal involvement that may often be overlooked. Renal biopsy plays a very significant role in diagnosis, and it should be reminded that early diagnosis and treatment may improve prognosis. Much larger multicenter studies would be required to establish the optimum therapeutic regimen.

Based on the experience reported here and on the literature published, the following considerations could be made:

1. That the benign nature of a monoclonal gammopathy does not exclude that it may be causing a secondary renal impairment.
2. That no patient should therefore be diagnosed MGUS without a prior minimal renal study consisting of sediment, proteinuria, and estimation of glomerular filtration rate and tubular function.
3. That, if renal involvement is detected, renal biopsy for verifying whether it is due to light chain deposition should be considered.
4. That, if deposition is found, chemotherapy should be considered, because renal impairment usually progresses to end-stage renal failure and stabilization of the renal condition has been reported after treatment.

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