Light chain deposition disease without glomerular proteinuria: a diagnostic challenge for the nephrologist

Antoine Sicard 1, Alexandre Karras 1, Jean-Michel Goujon 2,3, Christophe Sirac 3,4, Sébastien Bender 3,4, Delphine Labatut 5, Patrice Callard 6, Clémentine Sarkozy 7, Marie Essig 8, Philippe Vanhille 5, François Provot 9, Alain Nony 10, Dominique Nochy 11, Pierre Ronco 12, Frank Bridoux 3,13 and Guy Touchard 3,13

1Néphrologie, Hôpital Européen Georges Pompidou, Paris, France, 2Anatomo-Pathologie Rénale, CHU, Poitiers, France, 3Centre de référence amylose AL et autres maladies de dépôt d’immunoglobulines monoclonales, 4CNRS UMR 7276, Limoges, France, 5Néphrologie, CH, Valenciennes, France, 6Anatomo-Pathologie, Hôpital Tenon, Paris, France, 7Hématologie, Hôpital André Mignot, Versailles, France, 8Néphrologie, CHU, Limoges, France, 9Néphrologie, CHU, Lille, France, 10Néphrologie, CH, Bourges, France, 11Anatomo-Pathologie, HEGP, Paris, France, 12Néphrologie, Hôpital Tenon, Paris, France and 13Néphrologie, CHU, Poitiers, France

Correspondence and offprint requests to: Alexandre Karras; E-mail: alexandre.karras@egp.aphp.fr

Abstract

Background. Renal involvement in light chain (LC) deposition disease (LCDD) is typically characterized by nodular glomerulosclerosis and nephrotic range proteinuria. Rare cases of LCDD without glomerular symptoms have been reported, but clinical and pathological characteristics of this entity remain poorly described.

Methods. This multi-centre retrospective study included 14 patients with biopsy-proven renal LCDD and proteinuria <0.5 g/day at diagnosis.

Results. Baseline median serum creatinine was 281 (136–594) μmol/L, with a glomerular filtration rate of 20 (6–48) mL/min/1.73 m². A serum monoclonal immunoglobulin was detected in 12 cases and LC proteinuria only in 7, always of kappa isotype. Monoclonal gammopathy of undetermined significance/indolent multiple myeloma (MM) was diagnosed in nine cases, symptomatic MM in three cases. Hypertension was almost constant (10 of 14). Immunofluorescence studies of kidney biopsies showed linear kappa LC deposition along tubular basement membranes in all cases, with linear glomerular and vascular LC deposits in 11 and 10 patients, respectively. By light microscopy, tubulo-interstitial lesions were prominent in all patients and focal nodular glomerulosclerosis was only observed in two cases. Identification of LCDD led to initiation of chemotherapy in 12 cases. After a median follow-up of 25.5 months, five patients died and four progressed to end-stage renal disease. Renal response occurred in five of the eight patients who achieved sustained haematological response.

Conclusions. LCDD can cause severe renal dysfunction, despite the absence of glomerular symptoms. Early identification of the disease and introduction of a chemotherapy targeting the underlying plasma cell disorder may preserve long-term renal prognosis.

Keywords: light chain deposition disease, monoclonal gammopathy, myeloma, proteinuria, renal failure

Introduction

Randall-type monoclonal immunoglobulin deposition disease (MIDD) is a rare complication of plasma cell disorders [1, 2]. Light chain (LC) deposition disease (LCDD), the most common type of MIDD, is a multi-systemic disorder with nearly constant renal involvement. Renal lesions are characterized by non-amyloidotic linear deposition of monoclonal immunoglobulin LCs, most commonly kappa, along tubular basement membranes (TBMs) [3]. Linear LC deposition in
glomerular basement membranes, Bowman’s capsule, and around arteriolar myocytes is observed in most cases [4, 5]. Despite the invariable presence of tubular lesions, LCDD usually presents as a glomerular disease, which combines nephrotic range proteinuria, micro-haematuria, hypertension and renal insufficiency [6–8]. However, rare cases of LCDD with isolated symptoms of tubulo-interstitial nephropathy have been reported, but their clinical and pathological characteristics remain poorly described. LCDD with predominant tubulo-interstitial lesions represents a real diagnostic challenge for the nephrologist, because detection of monoclonal gammopathy is not routinely performed in non-proteinuric patients with renal failure. We herein describe the largest series of LCDD patients without glomerular proteinuria. Our study shows that these patients can develop severe kidney dysfunction, whose progression can be halted when suppression of the underlying B-cell clone has been achieved with appropriate chemotherapy.

MATERIALS AND METHODS

We retrospectively studied 14 patients with biopsy-proven renal LCDD and proteinuria ≤ 0.5 g/day. Patients were recruited in seven nephrology departments in France, between 1986 and 2011.

The diagnosis of LCDD was based upon the following findings on immunofluorescence (IF) study of kidney biopsy: (i) diffuse and linear deposits along TBMswith or without deposits in glomerular basement membranes or around arteriolar myocytes and (ii) positive staining of deposits with either the anti-kappa or anti-lambda conjugate, without staining with conjugates specific for Iga, γ and μ heavy chains. Patients were excluded from analysis when renal biopsy showed concurrent Amyloid Light chain (AL) amyloidosis. Kidney biopsy samples were processed by standard techniques for light microscopy (LM), IF and, in six cases, by electron microscopy, as previously described [9]. Sections were systematically stained with Congo red and examined under polarized light. By LM, lesions of nodular glomerulosclerosis were systematically recorded. The severity of tubular atrophy/interstitial fibrosis was graded based on a semi-quantitative scale, according to the percentage of affected renal cortex: 1–25%, mild; 26–50%, moderate; >50%, intense. Similarly, vascular lesions were graded on a scale from 0 to 3 (0, absent; 1+, mild; 2+, moderate; 3+, intense). For IF, 3-μm cryostat sections were stained with fluorescein isothiocyanate-conjugated rabbit antihuman γ, μ, α Ig heavy chain, C3, C1q, kappa and lambda LC (κ and λ LC) antibodies (Dako, Glostrup, Denmark). Intensity of fluorescence was graded on a scale from 0 to 3+. In six patients, ultra-thin sections were processed for EM studies and examined under a JEOL JEM-1010 electron microscope (Tokyo, Japan). Deposits were graded by EM on a scale from 0 to 3+ as previously described [9].

All patients underwent assessment of renal and haematological characteristics at baseline. The four variable Modification of Diet in Renal Disease (MDRD) study equations were used for the estimation of glomerular filtration rate (eGFR) [10]. Proteinuria was measured at least twice, on a 24-h urine collection. Hypertension was defined by systolic BP >140 mmHg or diastolic BP >90 mmHg or on-going anti-hypertensive therapy. In all patients, detection and characterization of serum and urine monoclonal Ig was performed using conventional electrophoresis and immunoelectrophoresis/immunofixation. Neophelemetric measurements of serum-free LC (FLCs) levels (Binding Site, Birmingham, UK) were available in six patients. Skeletal X-ray examination and bone marrow aspiration were performed in all patients. After obtaining patient and institutional review committee consents, total RNA was extracted from BM biopsies in four patients (Cases 1, 5, 9 and 11) and the monoclonal LC sequences were deduced and analysed as previously described [11]. Isoelectric points (pI) of the variable domains were estimated using the Expasy Software Compute pl/Mw (http://web.expasy.org/compute_pi/).

The diagnosis of multiple myeloma (MM) was assessed according to the International Myeloma Working Group criteria, reviewed in the recent ESMO Guidelines [12, 13]. MM stage was defined according to the Durie and Salmon staging system [14]. Monoclonal gammopathy of unknown significance (MGUS) was defined according to the criteria of <10% medullary plasmacytosis [13, 15].

Chemotherapy regimens received by each patient were recorded. Patient and renal survival was assessed at 1, 3 and 5 years, and/or at last follow-up. Haematological response was defined as a >50% decrease in the concentration of the serum monoclonal component (based on electrophoresis monoclonal spike and/or serum FLC levels). Renal response was defined as follows: complete response: improvement of eGFR to ≥60 mL/min/1.73 m²; partial response: increase of eGFR ≥50% with eGFR <60 mL/min/1.73 m²; minor response: increase of eGFR ≥25 and <50%; and no response.

Results involving continuous variables were expressed as mean values ± standard deviation if normally distributed or as the median and range if not normally distributed. Non-normally distributed continuous variables were compared using the Mann–Whitney U-test.

RESULTS

Baseline clinical characteristics

Table 1 summarizes the main clinical data of the 14 patients. Median patient age was 68 years (range 50–80 years); the male/female ratio was 8:6. At presentation, all patients had chronic kidney dysfunction, with a median serum creatinine level of 281 (136–594) μmol/L and a median eGFR level of 20 (6–48) mL/min/1.73 m². Of note, none of the patients presented with oligoanuric acute renal failure at LCDD diagnosis. Median proteinuria was 0.3 g/day (range 0.01–0.5 g/day) and micro-haematuria was found in only four patients. Conventional urinary electrophoresis was not performed in four patients because of the low level of proteinuria. For the remaining patients, median albuminuria was 0.285 g/L (range 0.04–0.35 g/L) by electrophoresis. Hypertension was present in 10 of 14 patients. None of the patients had symptomatic extra renal manifestations of LCDD.
A serum monoclonal (M) immunoglobulin was detected in 12 of 14 patients (86%). Isotypes were IgMκ (n = 2), IgAK (n = 2), IgGκ (n = 3) or isolated κ LC (n = 4). One patient had IgMκ and IgGκ bicalon gammapathy. A urine M-protein was identified in 8 of 14 (57%) patients (isolated κ LC, n = 7; IgGκ, n = 1). In six of the six patients tested for serum FLC, raised serum kappa FLC levels were observed, with a median of 427 mg/L (range 77–2400 mg/L) and a median kappa/lambda ratio of 55 (range 4.5–216). Five patients (36%) were diagnosed MGUS, with <10% of dystrophic plasma cells on BM smears. Seven patients met the recently adopted MM criteria, namely >10% plasma cells on BM examination and presence of an end-organ damage (kidney failure for all of them, lytic bone lesions for two patients). Median medullary plasmocytosis was 23% for MM patients (range 12–58). Among them, four patients had Stage I MM, three were diagnosed Stage II (n = 1) or Stage III (n = 2) MM. Waldenström macro-globulinaemia (WM) was identified in two patients (14%). There was no significant difference in serum creatinine levels between patients affected by MM or not. In Patients 1, 5, 9 and 11, molecular investigations showed heterogeneity of the secreted monoclonal κ LCs that contrasted with previous studies [21]. They belonged to the Vκ4, Vκ1, Vκ3 and Vκ2 subgroups, respectively, with no common sequence peculiarities except D–N mutation in the FR3 region of variable domains in Patients 1 and 11, revealing a potential N-glycosylation site (Figure 1). All the variable domains also displayed global positive charges at physiologic pH (pI: 8.97, 7.97, 8.01, 8.60, respectively).

### Pathological findings

By LM (Figure 2A–D), tubular lesions were constant and consisted mainly of diffuse TBM thickening, observed in 14 cases (Table 2). In eight patients, TBM wrinkling was observed, frequently associated with glomerular and vascular degenerative lesions (global glomerular sclerosis and arteriosclerosis). Duplication of TBM was observed in eight patients. Tubular atrophy and moderate to severe tubulo-interstitial fibrosis were constantly found. In Patient 14, a peculiar pattern of segmental micro-cystic dilatation of tubular lumens close to peritubular LC deposits was observed in the outer medulla (Figure 2B). Rare myeloma casts were observed within distal tubule lumens in one patient. Glomerular lesions were more heterogeneous: seven patients had ischaemic changes with >10% of global glomerular sclerosis. Diffuse mesangial hypertension was present in six cases. Nodular mesangial glomerulosclerosis was observed in only two cases, involving up to 50% of glomeruli and was associated with severe ischaemic lesions in the remaining glomeruli. Mild to intense arteriosclerosis was constant. Arteriolar deposits were detectable in seven patients. Of note, none of the patients displayed glomerular or vascular amyloid deposits.

By IF (Figure 2E and F), diffuse linear monoclonal κ LC deposits along TBM was invariably observed (Table 3). Linear LC deposits along the glomerular basement membranes and around arteriolar myocytes were identified in 11 and 10 cases, respectively. In five of the six patients in whom ultra-structural study was performed, typical linear, finely granular electron-
dense deposits were present along the outer aspect of TBM (Figure 3). In Patient 1, deposits were mainly sub-epithelial, on the inner aspect of the TBM. Peri-tubular deposits were accompanied by linear glomerular deposits in three patients, two of whom also displayed arteriolar deposits. No staining was observed with anti-\(\lambda\) LC conjugate in any patient.

**Treatment**

Chemotherapy was given to 12 patients, including seven with MM, two with WM and three with MGUS. Details of chemotherapy regimens are given in Table 4. Only one patient received high-dose melphalan followed by autologous stem cell transplantation (ASCT). A second line of chemotherapy was administered in three of the seven patients with MM and in one case of WM.

**Outcome**

The median follow-up period was 25.5 months (range 2–147 months) (Table 4).

**Patient survival.** Five patients, including three with MM, died at 2, 4, 14, 44 and 46 months. Causes of death were
infection (n = 2), cardiovascular events (n = 2) and unknown (n = 1). Overall patient survival was 86% at 6 months, 79% at 1 year and 60% at 3 years.

Haematological assessment. Haematological response to chemotherapy was assessed in 10 of the 14 patients (two did not receive chemotherapy and two had no detectable serum M-protein). Eight of 10 patients achieved a haematological response. No patient with MGUS progressed to MM.

Renal survival. During follow-up, none of the patients developed proteinuria >0.5 g/day. Only three patients required chronic haemodialysis therapy, immediately upon diagnosis. Among the 11 remaining patients, a significant (≥20%) decrease in serum creatinine level occurred in seven cases (Cases 2, 4, 6, 8, 10, 13 and 14). The death-censored renal survival was 89% at 1 year and 85% at 3 years. Median serum creatinine at last follow-up was 180 μmol/L (range 130–697 μmol/L; MDRD 30 mL/min/1.73 m², range 7–47). Among the eight patients who achieved haematological response, five also achieved a sustained renal response to therapy.

DISCUSSION

We report herein the largest series of biopsy-proven LCDD without significant proteinuria. In all previous reports of Randall-type MIDD, mean 24-h urine protein excretion was superior to 2.5 g. In the three largest LCDD series published to date, it reached the nephrotic range in 36–50% of cases [6–8]. Pozzi et al. [6] reported that only 16% of LCDD patients had <1 g/day proteinuria. In the recent study by Nasr et al. [7], only 3% of MIDD patients had non-significant proteinuria (<150 mg/day). As work-up for monoclonal gammopathy is not systematically performed in patients with non-proteinuric kidney disease, this atypical form of LCDD is probably under-diagnosed. Although the actual retrospective study cannot determine the prevalence of non-proteinuric LCDD, we can make the hypothesis that it concerns ~1% of all monoclonal Ig-related kidney disease, based on the published data of the Mayo Clinic group [7, 16].

Since presenting symptoms consisted of chronic kidney disease (CKD) with severe hypertension and low-grade
proteinuria, nephroangiosclerosis was the initially suspected diagnosis in most patients from the present series. If immunological tests had not revealed the presence of an associated monoclonal gammopathy, most of them would not have undergone kidney biopsy. Of note, 6 of 14 patients had no detectable spike or monoclonal component on serum protein electrophoresis or immuno fixation, and Bence Jones proteinuria was absent in 6 of 14 patients. This observation suggests that dysproteinemia is more difficult to detect in non-proteinuric LCDD than in other forms of LCDD, as showed by the comparison of our data with previously reported series (Table 5). In contrast, the FLC assay demonstrated raised FLC serum levels in all six tested patients, that matched the isotype found in renal deposits. Nephelemetric tests have been

<table>
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<th>Diagnosis</th>
<th>Chemotherapy</th>
<th>FU period</th>
<th>Death</th>
<th>eGFR</th>
<th>Renal response to therapy</th>
<th>Haematological response to therapy</th>
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<td></td>
<td>(Stage)</td>
<td>First line</td>
<td>Second line</td>
<td>Third line</td>
<td>HDT/ASCT</td>
<td>Months</td>
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<tr>
<td>1 MM (IIB)</td>
<td>VbMCP VbMCP</td>
<td>46</td>
<td>Y</td>
<td>46</td>
<td>6 HD</td>
<td>NR</td>
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<td>2 WM</td>
<td>RCD</td>
<td>6</td>
<td>N</td>
<td>18</td>
<td>24 MR</td>
<td>No</td>
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<td>3 MM (IIB)</td>
<td>MP</td>
<td>14</td>
<td>Y</td>
<td>14</td>
<td>13 HD</td>
<td>NR</td>
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<tr>
<td>4 MM (IIB)</td>
<td>VbMCP</td>
<td>4</td>
<td>Y</td>
<td>4</td>
<td>18 36 PR</td>
<td>Yes</td>
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<tr>
<td>5 MM (IB)</td>
<td>MD MD LD</td>
<td>98</td>
<td>N</td>
<td>48</td>
<td>34 NR</td>
<td>No</td>
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<tr>
<td>6 MM (IB)</td>
<td>BD</td>
<td>Yes</td>
<td>36</td>
<td>N</td>
<td>24 36 PR</td>
<td>Yes</td>
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<tr>
<td>7 MGUS</td>
<td>None</td>
<td>2</td>
<td>Y</td>
<td>2</td>
<td>7 HD</td>
<td>n/a</td>
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<td>8 MGUS</td>
<td>BMD</td>
<td>12</td>
<td>N</td>
<td>29</td>
<td>37 MR</td>
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<td>9 WM</td>
<td>MP CAVP</td>
<td>147</td>
<td>N</td>
<td>28</td>
<td>28 NR</td>
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<tr>
<td>10 MGUS</td>
<td>MP</td>
<td>39</td>
<td>N</td>
<td>36</td>
<td>47 MR</td>
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<tr>
<td>11 MM (IB)</td>
<td>VAD CTD MD</td>
<td>72</td>
<td>N</td>
<td>36</td>
<td>25 NR</td>
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<tr>
<td>12 MM (IB)</td>
<td>CP</td>
<td>7</td>
<td>N</td>
<td>11</td>
<td>7 NR</td>
<td>NA</td>
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<tr>
<td>13 MGUS</td>
<td>BD</td>
<td>15</td>
<td>N</td>
<td>22</td>
<td>30 MR</td>
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<tr>
<td>14 MGUS</td>
<td>None</td>
<td>44</td>
<td>Y</td>
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<td>8 16 n/a</td>
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</table>

HDT/ASCT, high-dose therapy followed by autologous stem cell transplantation; MM, multiple myeloma; WM, Waldenström macro-globulinaemia; MGUS, monoclonal gammopathy of undetermined significance; B, bortezomib; D, dexamethasone; V, vincristin; A, doxorubicin; T, thalidomide; C, cyclophosphamide; M, melphalan; L, lenalidomide; b, bis-chloroethyl nitrosourea (BCNU); P, prednisone; R, rituximab; FU, follow-up; HD, haemodialysis; n/a, non-adapted; NA, non-available.

*MDRD (mL/min/1.73 m²).

*Complete response (CR) = last eGFR >60 mL/min; partial response (PR) = ΔeGFR ≥50% and last GFR <60 mL/min; minor response (MR) = ΔeGFR >25 and <50%; no response (NR) = ΔeGFR <25%.

*More than 50% decrease in the concentration of the serum monoclonal component (based on electrophoresis monoclonal spike and/or serum FLC levels).
reported to show abnormal serum FLC concentrations in virtually all patients with LCDD [7]. Therefore, these findings suggest that the immunological work-up of patients with kidney disease should include a routine serum FLC assay, even in the absence of overt proteinuria.

MGUS is frequently diagnosed during the initial evaluation of a kidney disease, especially in elderly patients [14]. Its presence is usually considered as a serious argument to propose a kidney biopsy, when associated with other renal symptoms. The majority of kidney diseases related to monoclonal gammopathy present with significant proteinuria [16]. Myeloma cast nephropathy is usually due to high amounts of monoclonal LC proteinuria [17] and most cases of renal amyloidosis [18], monoclonal (Type 1) cryoglobulinaemia [19], Randall-cast nephropathy is usually due to high amounts of monoclonal LCs depends on glycosylation or structure peculiarities in κ LC variable domains [21] except for high pl values, a usual characteristic of LCDD LCs that could explain the granular deposits by charge interactions between cationic LCs and anionic heparan sulphate proteoglycans of basement membranes [22]. Interestingly, in Cases 1 and 11, the sequences of the variable domains differed from their germ-line counterparts by the appearance of a potential N-glycosylation site in the FR3 region. Intracellular glycosylation of the monoclonal κ LC of Patient 1 was previously confirmed with in vitro experiments [23]. Whether the pattern of tissue deposition of some κ LCs depends on glycosylation structure peculiarities of the variable domain remains to be determined, based on comparison with sequences of κ LC from LCDD patients with and without glomerular symptoms.

In this study, MM was found in 50% of cases, a percentage quite similar with what has been reported in previous large studies on LCDD [6–8] (Table 5). However, most patients had an indolent plasma cell or lymphoid disorder. The present series suggests that suppression of nephrotoxic monoclonal LCs has beneficial effects on kidney disease, even when LCDD is diagnosed in patients with advanced CKD. Six of the eight patients who achieved sustained haematological remission showed stabilization or improvement in GFR level, which indicates that chemotherapy is necessary in LCDD, even in the absence of an underlying life-threatening haematological malignancy. The International Kidney and Monoclonal Gammapathy Research Group recently introduced the term ‘Monoclonal Gammapathy of Renal Significance’ (MGRS), to highlight that most renal disorders in patients with monoclonal gammopathy are related to the secretion of toxic LCs [24], produced by ‘small dangerous B-cell clones’ [25]. The current diagnostic scheme that divides patients in ‘benign’ MGUS, smouldering myeloma without organ damage and aggressive MM fails to properly categorize the haematological disorders in these cases. Despite the lack of indication of chemotherapy to control tumour growth, urgent treatment is usually required to prevent renal deterioration and avoid recurrence after kidney transplantation [24]. For instance, several reports have shown the efficacy of bortezomib-based regimens [26] or

<table>
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<th>Table 5. Patients characteristics, compared with previous large LCDD series</th>
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<td>Present study</td>
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<tr>
<td>Number of patients</td>
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<td>Mean age</td>
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<td>Sex ratio (M/F)</td>
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<td>Mean serum creat at presentation</td>
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<td>Patients (%) with &gt;10% plasma cells on BM</td>
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<tr>
<td>Abnormal SPEP/SIFE (%)</td>
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<td>Abnormal UEPF/UIFE (%)</td>
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<td>κ LC deposition (%)</td>
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<tr>
<td>Hypertension (%)</td>
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<tr>
<td>24-h Proteinuria (g)</td>
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<tr>
<td>Presence of haematuria (%)</td>
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<tr>
<td>Mean follow-up (months)</td>
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<tr>
<td>Patients with stable/improved renal function (%)</td>
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<td>3-year renal survival (%)</td>
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high-dose therapy followed by ASCT on renal and vital outcomes in LCDD, including in patients failing to be classified as MM because of either <10% medullary plasmocytosis or absence of overt kidney dysfunction [27–30]. Based on these data, we think that the five MGUS patients of our study, presenting with <10% medullary plasmocytosis, should be diagnosed as MGRS, based on the presence of significant renal disease linked to the haematological disorder.

In the present series, death-censored renal survival at 3 years was higher than reported in a large previous LCDD study (85 versus 43%, respectively) [6], despite the fact that the initial renal function was very similar to what has been described before—mean serum creatinine 281 versus 335 μmol/L (Table 5). Although our cohort of patients is too small to draw firm conclusions, this observation may indicate a slower progression to ESRD for patients with tubulo-interstitial LCDD than for those with glomerular LCDD.

In conclusion, tubulo-interstitial LCDD without significant glomerular proteinuria is a severe and probably under-diagnosed renal complication of monoclonal gammopathies. Our study suggests that the diagnostic work-up in patients with chronic kidney disease of unknown origin should include careful search for monoclonal gammopathy, including measurements of serum FLCs. Kidney biopsy should be considered in patients with kidney dysfunction and abnormal levels of serum FLC, even without significant glomerular proteinuria, in order to rule out AL amyloidosis or LCDD with prominent tubulo-interstitial or vascular lesions that may require specific treatment.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have had no involvements that might raise the question of bias in the work reported or in the conclusions, implications or opinions stated. The results presented in this paper have not been published previously in whole or part, except in abstract format at the 2012 ERA–EDTA congress, Paris, France and at the 2012 Réunion Commune de la Société de Néphrologie et de la Société Francophone de Dialyse, Genève, Suisse.


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LCDD without glomerular proteinuria

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Calcium-sensing-related gene mutations in hypercalcaemic hypocalciuric patients as differential diagnosis from primary hyperparathyroidism: detection of two novel inactivating mutations in an Italian population

Piero Stratta, Guido Merlotti, Claudio Musetti, Marco Quaglia, Alessia Pagani, Cristina Izzo, Elisabetta Radin, Andrea Airoldi, Filomena Baorda, Teresa Palladino, Maria Pia Leone and Vito Guarnieri

1Department of Translational Medicine, Nephrology and Transplantation, University ‘Amedeo Avogadro’, Hospital ‘Maggiore della Carità’, Novara, NO, Italy, 2Department of Health Sciences, SCDU of Pediatrics, University ‘Amedeo Avogadro’, Hospital ‘Maggiore della Carità’, Novara, NO, Italy and 3Medical Genetics, IRCCS ‘Casa Sollievo della Sofferenza’ Hospital, San Giovanni Rotondo, FG, Italy

Correspondence and offprint requests to: Claudio Musetti; E-mail: claudio.musetti@med.unipmn.it

ABSTRACT

Background. Inactivating mutations of the calcium-sensing receptor (CaSR), of the G-protein subunit α11 (GNA11) and of the adaptor-related protein complex 2, sigma 1 subunit (AP2S1) genes are responsible for familial hypocalciuric hypercalcaemia (FHH). The aim of this study was to analyse prevalence and pathogenicity of CaSR, GNA11 and AP2S1 mutations in patients with an FHH phenotype and to compare them with a sample of patients with primary hyperparathyroidism (PHPT) in order to identify the most useful laboratory parameter for a differential diagnosis.

Methods. Patients with an FHH phenotype were studied with polymerase chain reaction amplification and direct sequencing of the entire CaSR, GNA11 and AP2S1 coding sequences. Novel mutations were introduced in a Myc-tagged human wild-type (WT) CaSR cDNA-expressing vector, and functional assay was performed on human embryonic kidney cells evaluating expression and function of mutated proteins.

Results. Among 16 FHH patients, none had an inactivating GNA11 or AP2S1 mutation while 3 (18.8%) carried a CaSR mutation and 10 (62.5%) at least one CaSR polymorphism. Within the latter group, 7 of 10 patients had more than one polymorphism (4.1 ± 2.1 per patient). Two novel CaSR mutations [c.2120A>T (E707V) and c.2320G>A (G774S)] were identified: the E707V mutation prevented CaSR expression (western blot), whereas the G774S mutation determined a reduced receptor sensitivity to calcium (IP3 assay). PHPT patients showed significantly (P < 0.001) higher serum calcium, parathyroid hormone, urinary calcium and calcium–creatinine clearance ratio (CCCR) and significantly lower serum phosphate than FHH ones.

Conclusions. FHH should be clearly differentiated from PHPT to avoid unnecessary surgery: CCCR could be a useful screening tool while genetic analysis should include the two novel