Biopsy-proven resolution of renal light-chain deposition disease after autologous stem cell transplantation

Ioannis Petrakis1, Kostas Stylianou1, Vasiliki Mavroedi1, Eleftheria Vardaki1, Spyridon Stratigis1, Stavros Stratakis1, Irene Xylouri2, Constantinos Perakis1, Constantina Petraki1, Lydia Nakopoulou4 and Eugene Daphnis1

1Department of Nephrology, Heraklion University Hospital, Crete Greece, 2Department of Haematology, Heraklion University Hospital, Crete Greece, 3Department of Pathology, Evaggelismos General Hospital, Athens Greece and 4Department of Pathology, University of Athens, Athens Greece

Correspondence and offprint requests to: Kostas Stylianou; E-mail: kstylianu@gmail.com

Abstract

Light-chain deposition disease (LCDD) is caused by an underlying clonal plasma cell dyscrasia in which monoclonal immunoglobulin light chains (LCs) are deposited in tissues, resulting in varying degrees of organ dysfunction. Autologous stem cell transplantation (ASCT) has been reported to stabilize renal function in patients with LCDD, but currently, no evidence of histopathologic resolution of LC deposition after ASCT exists. We present a patient, with severe renal dysfunction due to LCDD, who was treated with high-dose melphalan and ASCT that resulted in a significant and extended period of improved renal function. Four years after the initial improvement, the patient developed nephrotic range proteinuria, without any evidence of relapse of the plasma cell dyscrasia. At that time, a repeat renal biopsy showed complete resolution of LC depositions and development of extensive glomerulosclerosis, thus explaining proteinuria. To the best of our knowledge, this is the first report of a biopsy-proven resolution of renal LCDD following ASCT. A timely application of ASCT should be considered in LCDD to prevent deterioration of renal function in the long run.

Keywords: autologous stem cell transplantation; light-chain deposition disease; renal biopsy

Introduction

Light-chain deposition disease (LCDD) is caused by an underlying clonal plasma cell dyscrasia in which monoclonal immunoglobulin light chains (LCs), usually of a kappa isotype, are deposited in tissues resulting in varying degrees of organ dysfunction [1]. This disorder was originally described by Randall et al. [2] in 1976 with regard to two patients with end-stage renal disease (ESRD) with granular deposition of free LCs that did not stain with Congo red in kidney pathologic evaluation.

Accumulation of LCs in the kidney may involve glomeruli, tubules, interstitium and vessels, either independently or concurrently. LCDD is the most prevalent form of non-amyloid monoclonal immunoglobulin (Ig) deposition disease (MIDD). The other two forms of MIDD, the light- and heavy-chain deposition disease (LHCDD) and heavy-chain deposition disease (HCDD) have been more rarely reported in existing international literature, and in clinical and pathological terms, are close to LCDD [3,4].

On light microscopy, the commonest lesions reported in MIDD include nodular glomerulosclerosis, with or without thickening of the glomerular basement membrane (GBM), mesangial matrix expansion, thickening of the tubular basement membrane (TBM) and tubular atrophy. Although nodular glomerulosclerosis has been reported to be the most prevalent pathologic feature of LCDD [3], recent reports show that it is infrequently observed in patients with multiple myeloma (MM) as the underlying cause of LCDD (44%) [5], or in patients with LCDD associated with myeloma cast nephropathy (18%) as a hardly rare situation [6].

The hallmark of LCDD is the evidence of monoclonal LC deposition along the TBM, especially at the distal tubules and Henle's loops, by immunofluorescence (95% of patients). LC deposition is also evident along the GBM (82%), the vascular wall (63%) and the periphery of mesangial nodules (40%) [5]. Using electron microscopy, granular electron-dense deposits appear along the GBM (74%), the outer part of the TBM (56%) and the vascular wall (34%) [5].

Effective treatment of monoclonal plasma cell dyscrasia with high-dose chemotherapy and autologous stem cell transplantation (ASCT) has been reported to stabilize renal function and improve patient and renal survival [5–13]. In this report, we present a patient who developed severe kidney failure due to biopsy-proven LCDD with nodular LC deposits, who was treated with high-dose melphalan and ASCT, resulting in a significant and long-lasting improve-
ment of kidney function. Four years later, a second biopsy was performed due to reappearance of proteinuria, which showed resolution of nodular lesions and LC deposition that were replaced by fibrotic tissue. To the best of our knowledge, this is the first report of a biopsy-proven resolution of renal LCDD after ASCT.

Case report

A 49-year-old Caucasian female was referred to our department on February 2001 due to elevated serum creatinine (189 μmol/L) levels. The patient’s major complaint was fatigue, and her prior medical history was remarkable only for arterial hypertension of 6 months duration on enalapril. Physical examination revealed tachycardia (120 bpm) and well-controlled blood pressure. Complete blood count revealed normochromic normocytic anaemia. A screen for anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies and anti-double-stranded DNA (dsDNA) antibodies was negative. Urine examination was unremarkable except for a trace of proteinuria. Renal ultrasound showed increased echogenicity in both renal cortices. The patient was diagnosed as suffering from chronic kidney disease (CKD) of unknown aetiology, and treatment with enalapril continued.

Ten months later, the patient developed pedal oedema with mild proteinuria (0.5 g/day) and increased serum creatinine (415 μmol/L). She was found to have hypothyroidism secondary to autoimmune thyroiditis and was given thyroxin orally. In February 2002, the patient consented to a renal biopsy while serum creatinine levels had already risen to 619 μmol/L and urine protein to 2 g/day.

The biopsy specimen contained 45 glomeruli. Three glomeruli showed profound nodular appearance, 3 showed mesangial expansion and 24 demonstrated advanced ischaemic collapse of capillary loops with mesangial expansion and fibrosis extended at the perihilar area of Bowman’s capsule while the remainder (33%) were globally sclerotic (Figure 1). Renal tubules presented diffused atrophy and thickening of the TBM which was vividly stained with periodic acid–Schiff (PAS) stain. The renal interstitium was mildly fibrotic with a large focus of monocytic infiltration. Immunofluorescence showed increased deposition of kappa-LCs along the TBM, GBM, Bowman’s capsules and vascular walls, and within the nodular formations of the affected glomeruli. Congo red staining was negative. Urine and serum immunofixation disclosed a low titre of kappa-light chains. A bone marrow biopsy showed diffuse presence of mature, as well as immature plasma cells accounting for ~12% of the marrow cell population. In situ hybridization showed two plasma cell subpopulations; a dominant one that stained positively for kappa-LCs and a secondary one that stained positively for lambda-LCs. Based on these findings, the diagnosis of LCDD was made, and 2 months later, the patient was treated with high dose of melphalan (180 mg/m²) and ASCT.

One month after ASCT, serum creatinine levels dropped to 238 μmol/L and urine protein to 0.5 g/day; both stabilized at these levels over the following 4 years. Subsequently, in March 2006, increased levels of urine protein (3.9 g/day) were found during a routine urine examination. Despite treatment with enalapril and valsartan, the proteinuria persisted for the following months. A bone marrow biopsy at that time showed a polyclonal plasma cell population constituting 2–3% of the marrow cell population, mild increase in the cellularity of all hematopoietic cell lines and mild dysplastic abnormalities of the megakaryocytes. Serum and urine immunofixation tests were normal as well as a serum-free LC ratio (free kappa: 17.2 mg/L, free lambda: 13.4 mg/L, κ/λ ratio: 1.28). In December 2006, while serum creatinine was stable at 220 μmol/L and the patient’s proteinuria had further deteriorated (5 g/day), she underwent a second renal biopsy as a final effort to exclude LCDD relapse and to establish a histological diagnosis. The biopsy specimen contained 41 glomeruli. Thirty-three (80%) were globally sclerotic, and two showed segmental sclerosis (one of which with hyalinosel lesion). The rest presented with glomerulomegaly and increase of the mesangium and mainly of the mesangial matrix. The nodular lesions seen in the first biopsy were not present in the new one (Figure 2). Interstitial tissue showed focal fibrosis which extended over 30% of the cortical area and focal infiltration by many inflammatory mononuclear cells, while tubules were focally atrophic. Immunofluorescence was negative for kappa- or lambda-LCs, and Congo red staining was also negative. The diagnosis of focal segmental glomerulosclerosis secondary to prior renal injury was made.

Since the second biopsy, the patient’s renal function has gradually deteriorated and currently (7 years post-ASCT)

Fig. 1. (A) Nodular light-chain deposition disease (arrows), focus of tubular atrophy and interstitial fibrosis (arrowhead) with thickening and vivid periodic acid–Schiff stain of the basement membrane of the tubules at the same area, small epithelial cyst (asterisk) (PAS × 100). (B) Mesangial nodules with a regular distribution and size, characteristic of nodular light-chain deposition disease (arrows) (PAS × 400). (C) Immunofluorescence for kappa light-chain stains positive in the basement membrane of a glomeruli, the periphery of a mesangial nodule (arrow) and the basement membrane of some tubules (original magnification ×400).
has reached stage IV CKD, while proteinuria has stabilized <2 g/day with intensive renin–angiotensin system blockade.

Discussion

LCDD is characterized by kidney deposition of monoclonal immunoglobulin subunits which induces a dramatic accumulation of extracellular matrix, resulting in GBM and TBM thickening, nodular glomerulosclerosis and interstitial fibrosis. Structural variability of the LCs accounts for their pathogenicity and nephrotoxicity [3,4]. Amino acid substitutions in the variable portion of the abnormal LCs result in alterations of LCs conformation associated with their pathogenicity and nephrotoxicity [3,4]. Amino acid substitutions in the variable portion of the abnormal LCs result in alterations of LCs conformation associated with their pathogenicity and nephrotoxicity [3,4]. Amino acid substitutions in the variable portion of the abnormal LCs result in alterations of LCs conformation associated with their pathogenicity and nephrotoxicity [3,4]. Amino acid substitutions in the variable portion of the abnormal LCs result in alterations of LCs conformation associated with their pathogenicity and nephrotoxicity [3,4].

The consequent downstream effects involve alterations in the expression of matrix metalloproteinases and the production of extracellular matrix components, thus leading to interstitial fibrosis and eventually to CKD [17,18]. ASCT ablates the underlying bone marrow neoplasm, thus preventing the production of monoclonal LCs [19] and reversing the above-mentioned alterations.

LCDD carries a poor long-term prognosis, with an 8-year survival rate reaching 31%, in affected patients [5]. Risk factors related to worse renal and patient outcomes are the presence of multiple myeloma, LCDD associated with cast nephropathy, elevated serum creatinine (>330 μmol/L) at the time of renal biopsy and symptomatic extra-renal LC deposition [6]. It has recently been shown that LCDD and the associated renal dysfunction can be more effectively treated with ASCT compared to conventional chemotherapy alone [5,6,8,13]. This also holds true for our patient who had a significant, rapid and prolonged improvement of renal function with disappearance of LC deposits after ASCT. Resolution of nodular lesions and LC deposition has been previously reported in two patients with nephrotic syndrome and mild renal failure who were treated with prolonged chemotherapy [10,11]. Conversely, in the series reported by Royer et al. [13], a single patient who underwent a repeat kidney biopsy after successful treatment of LCDD still presented LC deposits in the kidney 3 years later. Interestingly, in the same study, other organ biopsies (skin, liver, heart) taken from other patients showed resolution of the deposits after successful treatment. It therefore seems likely that the kidney may be more prone to deposition before treatment and more resistant to resolution of deposits after successful treatment, compared to other organs. We would like to point out though that the kidney biopsy was done from the autopsy of a non-functioning kidney that had been removed during placement of a kidney graft. Moreover, the patient had been on dialysis before ASCT and during the next 3 years until kidney transplantation. Thus, the presence of LC in the removed kidney implies that (i) either the disease may have been active in histological terms, resulting in permanent loss of kidney function, or (ii) that complete loss of kidney function may impair its intrinsic reparative properties or (iii) simply that resolution of kidney deposits occurs over a longer period of time.

A very recent study has also shown clinical and biochemical response to treatment with bortezomib and dexamethasone in four patients with LCDD, while ASCT was additionally performed in three of them. Interestingly, proteinuria relapsed soon after bortezomib withdrawal in the patient who did not undergo ASCT, despite the sustained haematological response. The authors suggested that bortezomib may have acted not only by suppressing the toxic LCs, but also by inhibiting the nuclear factor kB (NF-kB) pathway and TGF-β production in the kidney, possibly explaining the reappearance of proteinuria. Nevertheless, demonstration of a bortezomib effect on the inflammation in renal parenchyma was not possible since subsequent renal biopsies were not performed [20].

Regarding the progression of CKD following treatment of the initial triggering factor (as in our patient), there is a ‘critical point’ beyond which renal injury is self-perpetuating and irreversible [12,21]. We believe that the initial delay in performing the renal biopsy (in order to set the diagnosis) and apply the appropriate treatment led to critical damage of renal tissue and hence to maladaptive glomerulosclerosis of the remaining nephrons. Our case as well as other cases in the literature demonstrate that deposition of monoclonal LCs in several organs can be (and should be) treated by high-dose therapy (HDT)-ASCT or newer therapies, even in the absence of overt myeloma, in order to improve organ survival and mortality rate.

Fig. 2. Resolution of light-chain deposition disease 4 years after treatment. (A) Most glomeruli are globally sclerotic and tubules appear with atrophy (PAS × 100). (B) Preserved glomeruli display mesangial expansion while the nodular lesions seen in the first biopsy have been resolved in the last biopsy (PAS × 400). (C) Immunofluorescence showed absence of staining for kappa light chains (original magnification ×300).
Nephrotic syndrome associated with invasive mole: a case report

Jae Won Yang1, Seung Ok Choi1, Bi Ro Kim1, Young Sub Kim1, Jong Myoung Yoo1, Min Seob Eom2 and Byoung Geun Han1

1Department of Nephrology and 2Department of Pathology, Yonsei University Wonju College of Medicine, 162 Ilsan-dong, Wonju, Kangwon-do, South Korea

Correspondence and offprint requests to: Byoung Geun Han; E-mail: neptune@yonsei.ac.kr

Abstract

Gestational trophoblastic disease describes a number of gynaecological tumours that originate in the trophoblast layer, including hydatidiform mole (complete or partial), placental site trophoblastic tumour, choriocarcinoma and gestational trophoblastic neoplasia (GTN). Invasive moles are responsible for most cases of localized GTN. Two cases of GTN previously reported in the literature exhibited membranous glomerulonephritis (MGN). However, histologic examinations in our case did not reveal evidence.

Nephrotic syndrome associated with invasive mole

In conclusion, due to the indolent nature of the disease and since renal LC accumulation can be completely reversed, early performance of renal biopsy and timely application of ASCT is of critical importance in maintaining renal function in LCDD.

Conflict of interest statement. None declared.

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