CASE REPORT

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Recovery from LCDD-associated Severe Liver Cholestasis: a Case Report and Literature Review

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ABSTRACT

Light chain deposition disease (LCDD) is a rare multisystemic disorder associated with plasma cell proliferation. It mainly affects the kidney, but liver and heart involvement may occur, sometimes mimicking the picture of systemic amyloidosis. Liver disease in LCDD is usually asymptomatic and exceptionally manifests with severe cholestatic hepatitis. We report the case of a 66-year-old female with κ-LCDD and cast nephropathy in the setting of symptomatic multiple myeloma who, after a first cycle of bortezomib-dexamethasone chemotherapy, developed severe and rapidly worsening intrahepatic cholestasis secondary to liver κ-light chain deposition. Intrahepatic cholestasis was attributed to LCDD on the basis of the liver histology and exclusion of possible diagnoses. Chemotherapy was maintained and resulted in progressive resolution of cholestasis. We report here an uncommon presentation of LCDD, with prominent liver involvement that fully recovered with bortezomib-based chemotherapy, and briefly review the relevant literature.

Key words: light chain deposition disease – myeloma – liver – cholestatic hepatitis.

Abbreviations: AKI: Acute kidney injury; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CMV: Cytomegalovirus; EBV: Epstein–Barr virus; GGT: gamma-glutamyl transferase; HSV: Herpes simplex virus; LC: light chain; LCDD: Light chain deposition disease; MIDD: Monoclonal immunoglobulin deposition disease; MM: Multiple myeloma.

INTRODUCTION

Randall-type light chain deposition disease (LCDD) is a rare complication of monoclonal gammopathies, characterized by tissue deposition of amorphous, granular, and non-Congophilic deposits of monoclonal immunoglobulin light chain (LC) on basement membranes [1, 2]. The diagnosis of LCDD requires histological demonstration of monotypic LC deposition by immunofluorescence and in some cases ultrastructural analysis of the involved organs or tissues. LCDD can occur in the context of isolated monoclonal gammopathy or of symptomatic multiple myeloma (MM) and Waldenström's macroglobulinemia. Light chain deposits are usually the κ (kappa) isotype and can affect almost all organs. Kidney disease is the more frequent manifestation, resulting in chronic kidney failure with glomerular proteinuria, and sometimes nephrotic syndrome. Heart, liver, gastrointestinal tract and peripheral nerves may also be involved [3–8]. Usually asymptomatic, liver involvement has been rarely reported in LCDD. In symptomatic patients, LCDD-associated liver involvement mainly manifests as cholestatic hepatitis [8–10] and is associated with high mortality.

We report herein a patient with myeloma-associated LCDD who developed rapidly progressive liver failure secondary to κ-light chain deposition, which rapidly recovered after hematological response following bortezomib-based chemotherapy.

CASE REPORT

A 66-year-old woman without significant past medical history was admitted to our department with asthenia and oliguria. Cardiac, pulmonary, abdominal and neurological physical examinations were normal. Blood tests showed acute

kidney injury (AKI) with serum creatinine of 1,879 µmol/L and urea of 90 mmol/L. Ultrasonography showed normal sized kidneys without urinary tract obstruction. Blood and urine tests revealed hypogammaglobulinemia (3.8 g/L) and glomerular proteinuria of 2.5 g/day. A serum and urine electrophoresis and immunofixation isolated monoclonal kappa LC gammopathy, with serum free kappa light chain excess of 6980 mg/L (normal <19.4 mg/L) with a kappa/lambda ratio of 377. Baseline liver tests and serum calcium were normal. The radiological evaluation demonstrated osteolytic lesions of the skull. The diagnosis of kappa light-chain myeloma was confirmed by bone marrow aspiration showing a 58% infiltration by dystrophic plasma cells.

Given the presence of glomerular proteinuria, a kidney biopsy was performed and demonstrated diffuse interstitial fibro-edema associated with acute tubular necrosis, and tubular casts. Immunofluorescence analysis showed intense linear kappa LC deposits on glomerular and tubular basement membranes and within arteriolar walls (Fig. 1A, B, C), associated with kappa LC casts within distal tubule lumens. Diagnosis of myeloma cast nephropathy associated with LCDD was established.

The patient was started on hemodialysis at admission, and received a first course of biweekly bortezomib (1.3 mg/m^2, administered subcutaneously on days 1, 4, 8 and 11, 21-days cycle) with dexamethasone (20 mg orally on days 1-2, 4-5, 8-9 and 11-12).

One month later, the patient developed atrial fibrillation without cardiac failure. Transthoracic echocardiography demonstrated hypertrophic cardiomyopathy (no pulmonary hypertension), without evidence of infiltrative cardiac involvement on MRI (left ventricle ejection fraction 75%). Concomitantly, blood tests showed severe cholestatic and cytolytic hepatitis (aminotransferases: ALT 183 UI/L [11-43]; AST 173 UI/L [12-3]; alkaline phosphatase, ALP 924 UI/L [5-76]; gammaglutamyl transpeptidase, GGT 718 UI/L [38-126] ; total bilirubin 129 µmol/L [1-17]; conjugated bilirubin 123 µmol/L [< 5]). Liver ultrasonography was normal without evidence of biliary obstruction. There was no history of alcohol abuse. Serological tests for hepatitis A, B and C, Ebstein-Barr virus (EBV), cytomegalic virus (CMV), and herpes simplex virus (HSV) were negative. Atrial fibrillation was treated by radiofrequency ablation. Hepatotoxicity of chemotherapy was suspected leading to interruption of bortezomib and dexamethasone along with other potentially hepatotoxic drugs (amlodipine, fluindione and furosemide). Despite these measures, liver tests progressively worsened with serum total bilirubin value reaching a maximum of 382 µmol/L at day 67. A liver biopsy was performed showing linear deposition of monotypic kappa light chain along the sinusoidal walls, confirming LCDD-associated liver involvement (Fig. 1D).

Bortezomib plus dexamethasone regimen was resumed and allowed complete haematological response of multiple myeloma after 8 courses (Fig. 2A). We observed a progressive and complete recovery of cholestatic and cytolytic hepatitis over the next 6 months (Fig. 2B), but renal failure did not improve. At 5 years from the initial diagnosis, the patient is in excellent condition with sustained complete hematological response but remains dialysis dependent.

DISCUSSION

Light chain deposition disease is a systemic disorder characterized by non-amyloid, amorphous linear deposition of monoclonal light chains in various organs. It occurs in

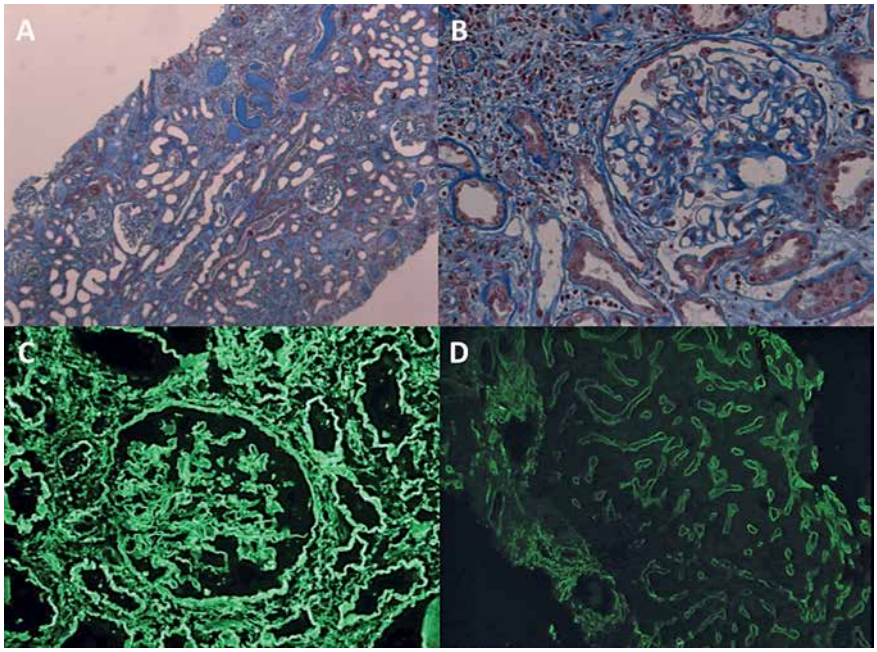

Fig. 1. (A, B) Light microscopy of kidney biopsy study showing interstitial expansion by diffuse fibro-edema, acute tubular necrosis, and fracturated polychromatophilic casts. (C) Immunofluorescence analysis of kidney biopsy showing intense linear kappa light chain deposition on vessels and glomerular and tubular basement membranes. (D) Immunofluorescence analysis of liver biopsy showing linear deposits of kappa light chains in the walls of the hepatic sinusoids.

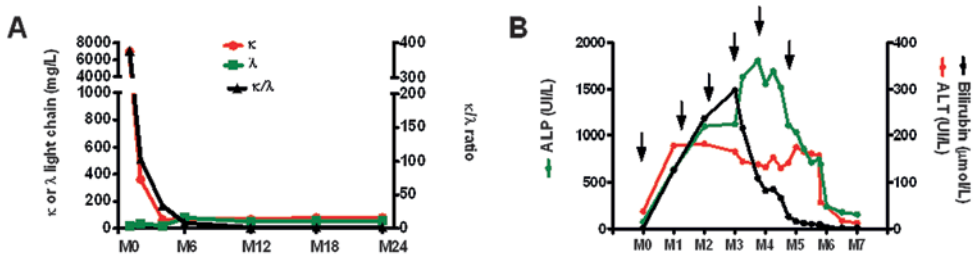

Fig. 2. Evolution of kappa, lambda light chain level and kappa/lambda ratio (A) and liver function tests (B) over time. (B) Arrows indicate the initiation of each bortezomib/dexamethasone cycle. ALP: alkaline phosphatase, ALT: alanine aminotransferase.

about 5% of patients with multiple myeloma. Myeloma has been classically reported as the underlying disease in most patients with LCDD [11, 12]. However, recent series indicate that a high proportion of LCDD cases are now encountered in patients without symptomatic plasma cell disorder, who meet the criteria for the recently introduced concept of monoclonal gammopathy of renal significance [1, 13]. Less frequently, LCDD may occur in the context of lymphoid hemopathy such as Waldenström disease [14]. Unlike AL-amyloidosis, LC deposits in LCDD, mostly the kappa isotype, do not stain with Congo red, and show a typical histological linear pattern along basement membranes by immunofluorecence microscopy, with a characteristic linear powdery punctate appearance by electron microscopy [15, 16].

Although liver involvement has been considered to be frequent in LCDD, on the basis of histological and post-mortem studies [4], severe liver complications have been rarely reported. In the literature, we identified 14 other cases of LCDD-associated liver failure (Table I). Multiple myeloma was the causative hematological disease in almost all cases, symptomatic in all cases. Intrahepatic cholestasis was the predominant presentation, associated with cytolysis in 33% of cases. The most frequent histological finding was linear deposits of monoclonal LC in the sinusoidal or perisinusoidal spaces with a predominance of kappa isotype (10/14 cases). In documented cases, death occurred in 5/7 patients within the first year after diagnosis. Liver injury developed in 2/15 cases after chemotherapy initiation [12, 17], suggesting an associated hepatotoxic mechanism.

Table I. Cases of LCDD-associated severe hepatitis from the literature

References	Sex	Age	Hematologic disease	Kidney involvement	Liver involvement	Type of liver involvement	Liver LC deposition	LC type	Chemo-therapy	Outcome
Droz et al. [9]	7 M	49 to 73	3/7 MM 1/7 MW 3/7 undefined	6/7 AKI 1/7 CKD	5/7 HM.	3/7 cholestasis 1/7 cytolysis	6/7 diffuse deposition	λ: 1/6 κ: 5/6	N/A	N/A
Faa et al. [10]	M	67	MM	No	HM Jaundice	Cholestasis Minimal cytolysis	Perisinusoidal space infiltration, portal tracts	λ	Mp	Alive at month 6
Casiraghi et al. [30]	M	60	AL Amyloidosis	No	HM	Cholestasis	Sinusoidal deposition and bile duct atrophy	λ	DEX	Dead at month 11
Michopoulos et al. [12]	M	36	MM	No	HM	Cholestasis Cytolysis	Perisinusoidal deposits	κ	VAD	Dead rapidly
Samanez et al. [17]	M	46	MM	AKI	HM	Cholestasis	Diffuse deposits on Disse spaces	κ	VAD	Dead at month 4
Ichikawa et al. [31]	F	62	MM	AKI	N/A	Cholestasis	Perisinusoidal space deposits	κ	DEX, PE	Dead rapidly
Weisel et al. [11]	F	78	MM	AKI	HM Jaundice	Cholestasis	Ischemic cholangitis Vascular LCDD of hepatic artery	N/A	MPL	Alive at month 3
Mena-Duran et al. [16]	F	81	MM	No	Jaundice	Cholestasis Minimal cytolysis	Perisinusoidal space	κ	DEX	Dead at month 1
Present case	F	65	MM	AKI	Normal	Major cholestasis Moderate cytolysis	Perisinusoidal space deposits	κ	VD	Alive at 5 years

AKI: acute kidney injury; BD: bortezomib-dexamethasone; DEX: dexamethasone; F: female;HD: hemodialysis; HM: hepatomegaly; M: male; MM: multiple myeloma; Mp: methylprednisolone; MPL: melphalan-prednisolone-lenalidomide; PE: plasma exchange; VAD: vincristine-adryamycin-dexamethasone; N/A: non applicable; κ: kappa; λ: lambda.

In the present case, hepatotoxicity of bortezomib was initially suspected. According to our knowledge, only three case reports of bortezomib-induced severe hepatitis have been reported in the literature [18–20], but no adverse event was reported in large studies (331 and 340 patients in APEX [21] and VISTA [22] trials, respectively). Moreover, the very progressive improvement of cholestasis despite continuation of bortezomib treatment strongly argues against bortezomib imputability. An infectious or a cardiac origin was also unlikely to account for liver failure, given the negativity of exhaustive infectious and viral screening, and the absence of right ventricular heart failure at echocardiography. Based on these findings, and given the liver biopsy results which undoubtedly showed evidence of LC deposition, we finally attributed liver failure as a specific manifestation of the disease in our patient. A control liver biopsy would have been interesting to analyze whether suppression of LC secretion with chemotherapy also resulted in clearance of liver LC deposits. Contrasting with liver response, kidney function was not restored. This discrepancy may be explained by the association of renal LCDD with LC cast nephropathy, a condition that has been reported to be associated with poor renal outcome before the era of novel anti-myeloma agents [23, 24]. However, recent data indicate that bortezomib-based regimens are associated with high hematological and renal response rates in LCDD, including patients with concomitant cast nephropathy [25]. Other factors may be involved in the present case, such as severity of interstitial fibrosis and vascular lesions.

Two other authors reported a favorable outcome evolution in LCDD patients with liver involvement, but without kidney disease (Table I). In the first case [10], the patient was treated with methylprednisolone alone, whereas in the second case [11], LC deposits were limited to hepatic arteries and did not affect sinusoidal walls. In this latter case, chemotherapy (melphalan-prednisolone-lenalidomid) was suspected to be the trigger of hepatotoxicity and the patient recovered after lenalidomid discontinuation.

Chemotherapeutic regimens containing the proteasome inhibitor bortezomib have shown efficacy and good tolerance profile in both AL amyloidosis [26–28] and Randall-type MIDD [25] but their effect on the clearance of LC tissular deposits, although possibly accepted, remains to be demonstrated. Interestingly, Komatsuda et al. [29] reported the disappearance of nodular mesangial lesions and disappearance of kappa light chain deposits in a patient with kidney LCDD under long-term chemotherapy. These data indicate that chemotherapy, a fortiori based on novel anti-myeloma agents, should be rapidly considered in LCDD patients with severe organ involvement, in order to rapidly induce efficient and sustained suppression of the pathogenic monoclonal LC. In LCDD, the achievement of a very good partial response (as assessed by the difference between involved and uninvolved LC of less than 40 mg/L) was recently demonstrated as an independent factor of renal prognosis [25].

CONCLUSION

Based on the literature review, symptomatic liver involvement in LCDD is associated with very poor patient survival. Our case confirms that, although uncommon, liver involvement may be a prominent and life threatening complication, that requires prompt diagnosis. Whether novel chemotherapy regimens, including bortezomib, may favorably influence outcome through rapid suppression of the underlying plasma cell clone remains to be confirmed.

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Authors' contribution: B.B. wrote the manuscript. J.S. participated in patient care and revised the manuscript. A.C. performed the pathology analysis and revised the manuscript. F.B. and J.F.S. revised the manuscript. J.F.A. wrote and revised the manuscript.

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