CASE REPORT

Portal hypertension related to light chain deposition disease of liver: an enlightening experience

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SUMMARY

A 55-year-old alcoholic man presented with firm hepatomegaly, ascites and markedly elevated alkaline phosphatase. He had a history of pulmonary tuberculosis. Work-up for malignancy was negative. Histological examination of liver showed extracellular deposition of pink amorphous material which is Congo red stain negative. Deteriorating renal function and nephrotic-range proteinuria were noted. Renal histology showed thickening of the glomerular and tubular basement membranes by non-congophilic deposits along with mesangial expansion. Bone marrow examination revealed patchy areas of pink amorphous deposits which are Congo red stain negative. Immunohistochemical staining of amorphous depositions in liver, kidney and bone marrow were positive for κ light chains. Serum-free light chain assay confirmed markedly elevated free κ -light chain. κ -light chain deposition disease is a systemic disease with universal renal involvement but rarely it presents as chronic cholestatic liver disease with portal hypertension and frequently associated with fatal outcome due to diagnostic delay.

BACKGROUND

Often marching on the usual track is misleading. Light-chain deposition diseases (LCDD) are last to occur in our mind when a long-standing alcoholic patient presents with evidences of portal hypertension. Marked rise of alkaline phosphatase (ALP) prompted us for a liver biopsy which showed amyloid-like deposition but Congo red stain negative. On search for systemic involvement both renal and bone marrow showed similar eosinophilic but Congo red stain negative deposition. Literature review led us to a possible diagnosis of LCDD which was confirmed by immune-histochemical staining and serum-free light chain assay (FLC). However, the patient's hepatic and renal function rapidly deteriorated during hospital stay probably because of delay in diagnosis and initiating therapy. Authors emphasize that LCDD should be considered in every patient of hepatic dysfunction even in the absence of renal involvement, when typical causes are excluded.

CASE PRESENTATION

A 55-year-old non-diabetic male patient with 6 months history of swelling of abdomen presented with exertional dyspnoea since a month. The patient is an alcoholic and was a smoker for 30 years but quit 3 years previously when he had pulmonary tuberculosis and received four-drug antitubercular regime for 6 months. No history of

fever, abdominal pain, jaundice, upper gastrointestinal bleeding, blood transfusion or alteration of bladder and bowel habit was present. Muscle wasting, bilateral pitting pedal oedema and jugular venous prominence were noted. His blood pressure was 110/80 mm Hg, pulse 84 beats/min and respiratory rate 24 beats/min. Abdominal examination showed firm non-tender hepatomegaly (span of 20 cm) without clinical splenomegaly and ascites without prominent abdominal veins. Examination of cardiovascular and respiratory system was unremarkable.

INVESTIGATIONS

Routine blood parameters showed haemoglobin 9.2 g/dl, total count 4300/dl (normal neutrophil and lymphocyte ratio), platelet count 1 lac/dl and erythrocyte sedimentation rate 74 mm in first hour. Liver function test revealed albumin 2 g/dl, globulin 2.8 g/dl, ALP 822 U/l (cut-off <390 U/l) and normal level of transaminases. Among the other relevant tests prothrombin time 12.1 s (international nationalised ratio 1.1), urea 61 mg/dl, creatine 2 mg/dl, sodium 131.2 mEq/l, potassium 4.13 mEq/l and corrected calcium 9.11 mg/dl. High serum aspartate aminotransferase of 4.2 U/l (cut-off <40 U/l) was found. Ultrasonography suggested coarse hepatomegaly, spleen 12 cm and portal vein diameter 10 mm with reduced phasic variation of venous flow with respiration. Gall bladder varices and recanalisation of umbilical vein were noted. Both the kidneys were normal in size and cortical echogenicity. Serological markers for hepatitis B, C and HIV were negative. Echocardiography showed diastolic dysfunction. Upper gastrointestinal endoscopy revealed early oesophageal varices. Contrast-enhanced CT of abdomen failed to demonstrate any hepatic parenchymal space occupying lesion or extrahepatic biliary obstruction. Echocardiography of heart was normal except diastolic dysfunction. Tumour markers for hepatocellular carcinoma were within normal limits. Histological examination of liver (figure 1) reported abundant pink homogeneous peri-sinusoidal deposits almost replacing hepatocytes and compressing bile ductules and portal tracts along with Kupffer cell hyperplasia. A definite diagnosis of amyloidosis (AL) could not be given as the homogeneous deposition was Congo red stain negative. Urine examinations showed 3+ proteinuria and total urinary protein excretion was 3.5 g in 24 h. Histological examination of the kidney (figure 2) shows global thickening of the glomerular and tubular basement membranes by non-congophilic amorphous materials along with

To cite: Talukdar A, Mukherjee K, Khanra D, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-009553

Figure 1 (A) Light microscopic examination of liver tissue showing abundant pink homogeneous material almost replacing the normal hepatocytes (H&E, ×50). (B) Extracellular eosinophilic peri-sinusoidal deposits compressing hepatocytes, bile ductules and portal tracts along with Kupffer cell hyperplasia (H&E, ×400).

mesangial expansion. Bone marrow examination revealed (figure 3) normal trilineage of haematopoiesis including 5% plasma cells with patchy areas of pink amorphous deposits which are Congo red stain negative. Congo red stain is highly specific for AL and its negativity raised the possibility of monoclonal immunoglobulin deposition diseases (MIDD). Serum and urine protein electrophoresis (PEL) with immune-fixation revealed no monoclonal peak. No osteolytic lesion was observed on skeletal surveys. Immunohistochemical stains revealed that eosinophilic depositions in the liver, kidney and bone marrow were composed of κ light chains. Serum FLC confirmed markedly elevated free κ -light chain of 602 mg/l (normal 3.5–20 mg/l).

DIFFERENTIAL DIAGNOSIS

- ▶ Chronic alcoholic liver disease with hepato-renal syndrome
- ▶ Hepatocellular carcinoma
- ▶ Cardiac cirrhosis
- ▶ AL of liver

TREATMENT

The long array of baffling results delayed us to reach a definitive diagnosis and the patient was maintained on propranolol,

spironolactone and intermittent therapeutic drainage of ascitic fluid. As the patient could not afford bone marrow stem cell transplant, Bortezomib-based induction chemotherapy was advised from haemato-oncology department. The patient refused chemotherapy.

OUTCOME AND FOLLOW-UP

Within hospital stay the general condition of the patient worsened. Despite supportive management his deteriorating renal and liver function went unabated. The patient could afford neither definitive chemotherapy nor dialysis and subsequently the patient was lost to follow-up.

DISCUSSION

MIDD are characterised by non-amyloid deposition of immunoglobulin in various organs leading to dysfunction.¹ It can be either LCDD or light-and heavy-chain deposition disease or heavy-chain deposition disease (HCDD).^{2–3} Although first recognised by Antonovych *et al*⁴ in 1974, LCDD was first described by Randall *et al*⁵ in 1976. The median age at diagnosis for LCDD is 58 years with male preponderance and the median duration of survival is approximately 4 years.⁶ The most

Figure 2 (A) Light microscopic examination of renal tissue showing extensive interstitial deposition of eosinophilic extracellular material and thickening of tubular basement membrane with tubular casts (H&E, ×100). (B) A representative glomerulus showing thickening of glomerular basement membrane with mesangial deposition of eosinophilic materials (H&E, ×400).

Figure 3 (A) Light microscopic examination of bone marrow biopsy showing plasma cell-rich area with patchy areas of extracellular eosinophilic accumulation (Leishman stain, $\times 400$). (B) Eosinophilic material with a Cumulus cloud-like appearance in the bone marrow (Leishman stain, $\times 400$).

commonly involved organ by LCDD is the kidney and other organs such as liver, heart, nerves, lympho-reticular organs, lung, skin and the brain.⁷

Renal involvement of LCDD is characterised by more conspicuous tubular lesions than the glomerular damage.⁸ Nodular glomerulosclerosis is the most characteristic glomerular lesion of LCDD but was absent in our case.⁸ Although expansion of the mesangial extracellular matrix (ECM) was observed in our case it is more associated with HCDD.⁹ Despite extensive renal damage the patient was normotensive. Liver involvement of CDD includes hepatomegaly out of proportion to liver enzyme.¹⁰ Liver involvement in LCDD has been reported even in the absence of renal manifestation.^{11–13} LCDD presenting with features of portal hypertension is rare in the literature.^{13–15} Portal hypertension in our case might be explained by the presence of abundant deposits in the space of Disse leading to sinusoidal obstruction of the portal venous system. An elevated jugular vein with diastolic dysfunction noted in echocardiography may be attributed to cardiomyopathy due to deposition of light chains albeit tissue diagnosis could not be made. LCDD involving heart can give rise to congestive heart failure to arrhythmias.¹⁶ LCDD is associated with monoclonal gammopathies of uncertain significance or multiple myeloma in 17% and 58% of cases, respectively, none of which were present in our case.¹⁷

Combination of serum and urine PEL and imminofixation has 77.85% sensitivity for detection of LCDD.¹⁸ With addition of serum FLC the sensitivity for diagnosis of LCDD goes up to 83.3% which confirmed our diagnosis.¹⁸ In our case, the immune-histochemical staining for light chain was consistent with the most common variety that is, κ -LCDD. In AL the depositions show immune-reaction with anti-sera for AL protein and amyloid P component.¹⁸ Electron microscopic identification of granular deposits favours a diagnosis of LCDD in contrast with β -pleated fibrillar deposits found in AL, which we could not employ.¹⁹ AL mostly represents $V_{\lambda}VI$ containing acidic residues and gets easily stained with Congo red through electrostatic interactions.²⁰ Whereas, approximately 80% cases of LCDD over-represent $V_{\kappa}IV$ light chains which possess

hydrophobic residues at a longer CDR1 loop and are typically Congo red stain negative.²⁰ N-glycosylation of the polar residues increases propensity to precipitate in tissues leading to absent light chain restriction in the serum and urine in 15–30% of patients such as in our case.²¹ Pathogenic LC may stimulate mesangial cells to secrete ECM components through transforming growth factor- β . AL lack this feature.²² Treatment options for LCDD are not standardised but high-dose melphalan followed by autologous stem cell transplant (HDM/SCT) has been employed successfully.²³ Recently bortezomib containing induction chemotherapy with or without dexamethasone is seen to attain a complete haematological remission and ameliorate renal dysfunction associated with LCDD.^{24–25}

Learning points

- ▶ Congo red stain negative pink amorphous extracellular deposition can be seen in light-chain deposition diseases (LCDD) and other monoclonal immunoglobulin deposition diseases.
- ▶ LCDD should always be kept in mind while working up a case of chronic liver disease with features of cholestasis and portal hypertension because delay in diagnosis carries dismal prognosis.
- ▶ Patients of LCDD should be screened for plasma cell dyscrasias including multiple myeloma due to their frequent association.

Contributors AT and MS were the treating physicians. KM and DK assisted with the work-up and manuscript writing.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Buxbaum JN, Chuba JV, Hellmann GC, *et al*. Monoclonal immunoglobulin deposition disease: light chain and light and heavy chain deposition disease and their relation to light chain amyloidosis. *Ann Intern Med* 1990;112: 455–64.
- 2 Preud'homme JL, Morel-Maroger L, Brouet JC, *et al*. Synthesis of abnormal heavy and light chains in multiple myeloma with visceral deposition of mono-clonal immunoglobulin. *Clin Exp Immunol* 1980;42:545–53.
- 3 Aucouturier P, Khamlichi AA, Touchard G, *et al*. Brief report: heavy-chain deposition disease. *N Engl J Med* 1993;329:1389–93.
- 4 Antonovych TT, Lin RC, Parrish E, *et al*. Light chain deposits in multiple myeloma. *Lab Invest* 1974;30:370A.
- 5 Randall RE, Williamson WC Jr, Mullinax F, *et al*. Manifestations of systemic light chain deposition. *Am J Med* 1976;60:293–9.
- 6 Pozzi C, D'Amico M, Fogazzi GB, *et al*. Light chain deposition disease with renal involvement: clinical characteristics and prognostic factors. *Am J Kidney Dis* 2003;42:1154–63.
- 7 Pozzi C, Locatelli F. Kidney and liver involvement in monoclonal light chain disorders. *Semin Nephrol* 2002;22:319–30.
- 8 Sanders PW, Herrera GA, Kirk KA, *et al*. Spectrum of glomerular and tubule-interstitial renal lesions associated with monotypic immunoglobulin light chain deposition. *Lab Invest* 1991;64:527–37.
- 9 Ronco PM, Alyanikian M, Mougenot B, *et al*. Light chain deposition disease: a model of glomerulosclerosis defined at the molecular level. *J Am Soc Nephrol* 2003;12:1558–65.
- 10 Nath SV, Peiris M, Bishton MJ, *et al*. Light chain deposition disease presenting as massive hepatomegaly. *Pathology* 2010;42:307–10.
- 11 Gireli C, Giovanni L, Rocca F. Light chain deposition disease of the liver. *Eur J Gastroenterol Hepatol* 1999;10:429–30.
- 12 Faa G, Van Eyken P, De Vos R, *et al*. Light chain deposition disease of the liver associated with AL-type amyloidosis and severe cholestasis. A case report and literature review. *J Hepatol* 1991;12:75–82.
- 13 Pelletier G, Fabre M, Attali P, *et al*. Light chain deposition disease with hepatomegaly: an association with amyloid-like fibrils. *Postgrad Med J* 1988;64:804–8.
- 14 Mignon F, Morel-Maroger L, Cerf M, *et al*. Depots hepatiques et renaux de chaines legeres kappa revelateurs d'une dysglobulinemie. *Nephrologie* 1980;1:167–70.
- 15 Ganeval D, Mignon F, Preud'Homme JL, *et al*. Depot de chaines legeres et d'immunoglobulines monoclonales: aspects nephrologiques et hypotheses physiopathologiques. *Act Nephrol Hop Necker* 1981;1:179–214.
- 16 Toor AA, Ramdane BA, Joseph J, *et al*. Cardiac non-amyloidotic immunoglobulin deposition disease. *Modern Pathol* 2006;19:233–7.
- 17 Lin J, Markowitz GS, Valeri AM, *et al*. Renal monoclonal immunoglobulin deposition disease. The disease spectrum. *J Am Soc Nephrol* 2001;12:1482–92.
- 18 Katzmann JA, Kyle RA, Benson J, *et al*. Screening panels for detection of monoclonal gammopathies. *Clin Chem* 2009;55:1517–22.
- 19 Preud'homme JL, Aucouturier P, Touchard G, *et al*. Monoclonal immunoglobulin deposition disease (Randall type). Relationship with structural abnormalities of immunoglobulin chains. *Kidney Int* 1994;46:965–72.
- 20 Denoroy L, Déret S, Aucouturier P. Overrepresentation of the V_kIV subgroup in light chain deposition disease. *Immunol Lett* 1994;42:63–6.
- 21 Ganeval D, Noel LH, Preud'homme JL, *et al*. Light-chain deposition disease: its relation with AL-type amyloidosis. *Kidney Int* 1984;26:1–9.
- 22 Herrera GA, Russell WJ, Isaac J, *et al*. Glomerulopathic light chain-mesangial cell interactions modulate in vitro extra-cellular matrix remodeling and reproduce mesangiopathic findings documented in vivo. *Ultrastruct Pathol* 1999;23:107–26.
- 23 Weichman K, Dember LM, Prokava T, *et al*. Clinical and molecular characteristics of patients with non-amyloid light chain deposition disorders, and outcome following treatment with high-dose melphalan and autologous stem cell transplantation. *Bone Marrow Transplant* 2006;38:339–43.
- 24 Minarik J, Scudla V, Tichy T, *et al*. Induction treatment of light chain deposition disease with bortezomib: rapid hematological response with persistence of renal involvement. *Leuk Lymphoma* 2012;330:330–1.
- 25 Kastritis E, Migkou M, Gavriatopoulou M, *et al*. Treatment of light chain deposition disease with bortezomib and dexamethasone. *Haematologica* 2009;94:300–1.

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