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Clinical Report

Kidney light chain disease in patients with the acquired immunodeficiency syndrome

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Abstract
Light chain deposit disease (LCDD) is a rare condition caused by deposition of overproduced monoclonal light chains and has been frequently related to multiple myeloma or lymphocytic disorders. LCDD in association with human immunodeficiency virus (HIV) has only been described twice in the literature and is thought to result from HIV direct/indirect effects on B and T-cell populations, leading to chronic immune activation with paraprotein production. We report a renal LCDD case diagnosed at autopsy in a severely immunodepressed HIV patient and analyse renal histopathology of 18 HIV patients who had an autopsy in our department between 2000 and 2010.

Keywords: HIV; light chain deposit disease (LCDD); renal pathology

Introduction

Human immunodeficiency virus (HIV) infection is associated with renal disease [1, 2]. The most frequently observed histopathological manifestations being HIV-associated nephropathy (HIVAN), immune complex glomerulonephritis, non-collapsing focal segmental glomerulosclerosis, thrombotic microangiopathy, tubulo-interstitial nephritis and antiretroviral therapy-associated tubulopathy. HIVAN is more frequent in blacks, whereas immune complex glomerulonephritis usually occurs in Caucasian patients; the other three diseases are rare ($<$1%). Although HIV is associated with severe dysregulation of the immune system, only two cases of light chain deposits disease (LCDD) in HIV patients have been reported in the literature. We describe here the third renal LCDD case diagnosed at autopsy in a severely immunodepressed HIV patient.

Case report

A 34-year-old man from the Netherlands Antilles, who had been in Geneva for 2 months, was admitted to hospital in a confused state. An acute respiratory distress syndrome required immediate mechanical ventilation. Chest X-ray revealed bilateral interstitial infiltrates. The patient was cachectic, hypothermic (31.2°C), normotensive (blood pressure: 117/67 mmHg) and oliguric. Laboratory tests showed increased white cell count (13 900 per mm^3 with 12% neutrophils), severe hypochromic regenerative anaemia (Hb 30 g/L; reticulocytes 0.148%; ferritine 1392 μg/L), thrombopenia (119 000/mm3), impaired coagulation (TP 46%, PTT 47.8 s, fibrinogen 6.4 g/L) and severe renal failure (serum creatinine 856 μmol/L; urea 88.6 mmol/L; hyperkalemia 7.4 mmol/L), with metabolic acidosis (pH 7.19; HCO_3 7.7 mmol/L). The kidneys were small and hyperechogenic, without pelvicalyceal dilatation. Imipenem therapy and haemodialysis were initiated.

HIV serology returned positive, with a CD4 cell count of 24/μL and a viraemia of 64 000 copies per mL. Hepatitis B virus and hepatitis C virus serologies were negative. Abacavir, Efavirenz and Atazanavir were added to imipenem. On Day 7, bronchoalveolar lavage fluid revealed *Pneumocystis jirovecii* and blood cultures were positive for methicillin-sensitive *Staphylococcus aureus*. Trimethoprim and sulphametoxazol were added. Immunologic tests revealed hypergammaglobulinaemia (IgG 23.20 g/L; kappa 230 mg/L; lambda 368 mg/L) without evidence of monoclonality and the presence of antineutrophil cyctoplasmic antibody (1/80) and anti-S-nuclear antibodies (1/2500).

On Day 17, nosocomial pneumonia with *Stenotrophomonas maltophilia* was diagnosed and Piperacillin and Tazobac were added. On Day 18, the patient developed a right pneumothorax complicated haemothorax. He died on Day 24 from massive haemorrhage during a tracheotomy.

At autopsy, massive bilateral chronic pneumonia was diagnosed in the presence of *P. jirovecii* and Cytomegalovirus. An HIV lymphadenitis pattern B was identified. Polyclonal plasmacytosis was observed in the bone marrow. Infrequent microglial nodules compatible with an HIV encephalopathy were found in brain. Kidneys were macroscopically normal (left kidney weight: 190 g; right kidney weight: 160 g). Light microscopy showed a glomerular mesangial matrix expansion with segmental mesangial cell proliferation (Figure 1A and B). Diffuse and moderate interstitial fibrosis with tubular atrophy was also noted. No significant tubular lesions were

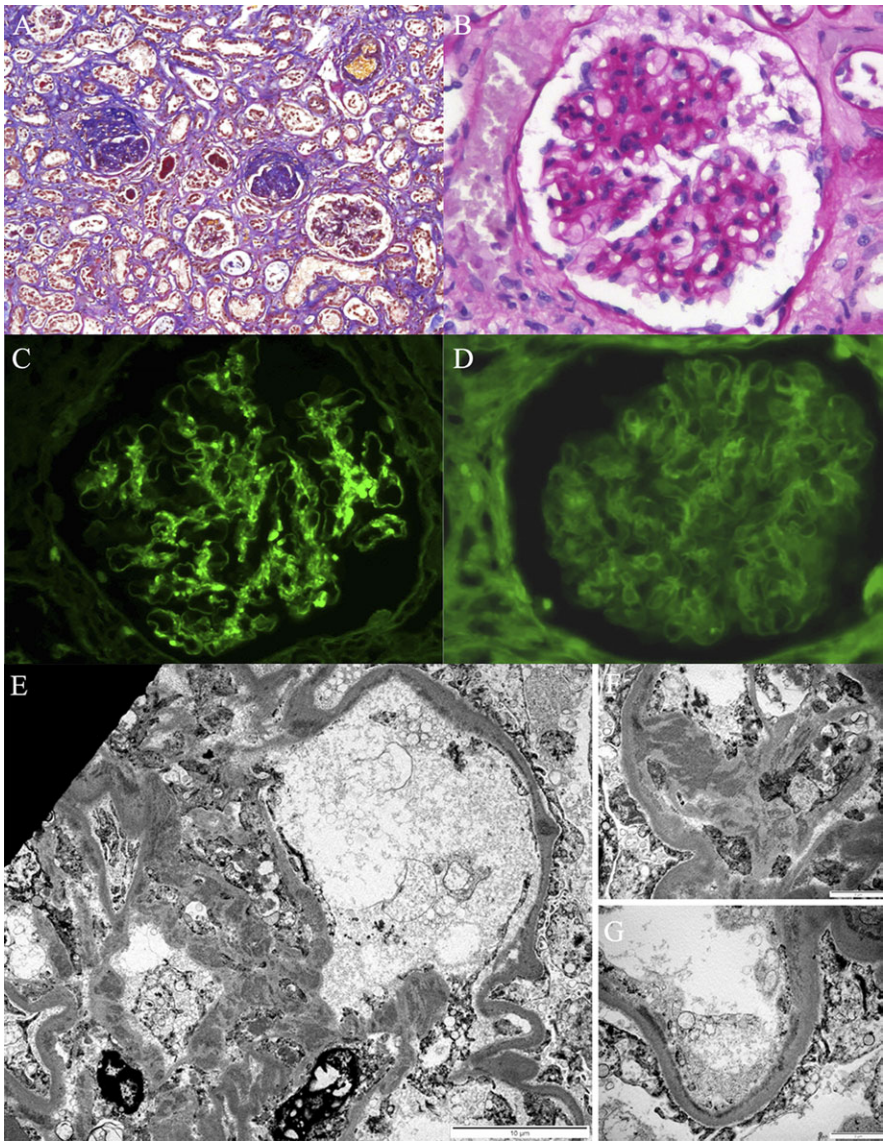

Fig. 1. Renal microscopical examination. (**A** and **B**) (Light microscopy): Glomerular mesangial matrix expansion, Trichrome staining (original magnification ×65) and Periodic acid-Schiff staining (original magnification ×260). (**C** and **D**) (Immunofluorescence): Kappa light chain deposition within the mesangium and along the glomerular capillary loops. Lambda light chain negativity as a control (original magnification ×100). (**E**–**G**) (Electron microscopy) Granular dense osmiophilic deposits in mesangial and sub-endothelial areas (original magnification ×3400 and ×10 500 on Philips CM10).

observed. Immunofluorescence revealed kappa light chain deposition within the mesangium and along the glomerular capillary membranes (Figure 1C and D). No deposits were observed along the tubular basement membranes. Electron microscopy identified numerous dense granular osmiophilic deposits, localized in the mesangial and sub-endothelial areas (Figure 1E and F). A polymerase chain reaction (PCR) analysis performed on frozen renal tissue confirmed the presence of kappa monoclonality, establishing the diagnosis of renal kappa LCDD. It should be noted that we were not able to demonstrate kappa monoclonality in bone marrow and lymph nodes using immunohistochemistry and PCR analyses on formalin-fixed samples.

Discussion

This case illustrates the diagnosis, at autopsy, of a renal LCDD in a severely immunodepressed HIV patient. Whereas renal diseases in particular glomerulopathies, are not uncommon in HIV patients, renal LCDD is rarely reported in the literature (Table 1). Thus, Berliner *et al* [3] recently reported a cohort study of 152 HIV-infected patients, the majority (91%) of whom were Afro-Americans, who underwent renal biopsy. The most frequent diagnoses were HIVAN (35%) and non-collapsing focal segmental glomerulosclerosis (22%); only one LCDD case was detected. In a similar series of biopsies performed between 1995 and 2011, no cases of LCDD were described [4–7]. A case report, published in 1992 by Shimamura *et al* [8] described the case of a 19-month-old HIV boy who, at 4 months of age, suffered a *P. jirovecii* pneumonia, with unexplained persistent proteinuria. The renal biopsy demonstrated LCDD with mesangiosclerosis, kappa light chain deposition along the tubular basal membranes and glomerular and tubular granular electron-dense deposits. Quantitative serum immunoelectrophoresis revealed hypergammaglobulinemia, albeit without evidence of monoclonality.

In our case, the renal diagnosis was made at autopsy. It is interesting to note that, in a large prospective autopsy study published in 2001, among the 239 patients who died of AIDS between 1981 and 1989, 102 had a nephropathological finding, but no renal LCDD case was diagnosed [9]. Similarly, in two other published necropsy studies, analysing renal involvement of 80 and 61 HIV patients who died between 1984 and 2006 and between 1984 and 1997, respectively, no LCDD case was reported [10, 11]. Therefore, we were interested to analyse the renal histopathological patterns of HIV patients at autopsy in our institute. Clinical records and renal pathological samples from 18 HIV patients (14 men and 4 women) who died between 2000 and 2010 were studied (Table 2). Optical microscopy and immunohistochemistry was performed on each renal sample. Electron microscopy was performed only in certain cases. No renal LCDD could be diagnosed. It is interesting to note that two patients (patient no. 7 and 13) had biological and clinical characteristics similar to our patient, i.e. CD4 levels lower than 50/μL and no previous therapy. In these two cases, mesangiopathy/mesangiosclerosis was observed, however, without any immunofluorescence glomerular or tubular light chain deposition nor electron microscopy granular osmiophilic deposits.

HIV-seropositive patients may have a higher incidence of monoclonal gammopathy of undetermined significance (MGUS) than their HIV-seronegative counterparts [12]. Thus, some of these patients present with transient paraproteinemia, while others have persistent paraproteins, which may or may not be associated with true plasma cell malignancies [13]. In most cases where it was analysed, the paraprotein contained high-titre anti-HIV activity, suggesting that an antigen-driven process in response to HIV infection may contribute to the early development of plasma cell disorders in these patients. Indeed, HIV infection leads, in addition to the progressive depletion and dysfunction of $CD4^+$ T cells, to extensive defects in the humoral arm of the

Table 1. Review of the literature: renal diagnosis of HIV patients (biopsy and autopsy series)

References	Biopsy/autopsy cases	LCDD	Glomerular/tubulointerstitial diseases	Vascular diseases	Others
Berliner AR *et al.* 2008 [3]	152/0	1	117/16	13	5
Cosgrove CJ *et al.* 2002 [4]	12/0	0	7/5	0	0
Gerntholtz TE *et al.* 2006 [5]	99/0	0	89/5	5	0
Williams DI *et al.* 1998 [6]	13/4	0	13/1	2	1
Gutiérrez E *et al.* 2007 [7]	27/0	0	27/0	0	0
Shimamura T *et al.* 1992 [8]	1/0	1	0/0	0	0
Hailemariam S *et al.* 2001 [9]	0/102	0	6/71	18	7
Nicolau Laparra MC *et al.* 2010 [10]	0/80	0	24/47	0	9
Giner V *et al.* 2004 [11]	0/61	0	20/34	0	7

Table 2. Clinical data (determined at the time of hospitalization before death) and renal diagnosis (necropsy findings) of 19 HIV patients who died in our hospital between 2000 and 2010[a]

Patient number	Origin	Gender	Age	CD4 (/μL)	Tritherapy	Cause of death	Histologic diagnosis
1.	ANT	M	34	24	No	Pneumonia with *Pneumocystis jirovecii*	LCDD
2.	WA	M	46	498	9 years	Heart failure	Nephroangiosclerosis
3.	C	M	52	143	20 years	Pancreatic adenocarcinoma	Nephroangiosclerosis
4.	C	F	49	222	Yes	Pulmonary consolidation with oedema and alveolar haemorrhage	Segmental mesangiosclerosis, without deposits (κ/λ/IgA/IgG)
5.	C	M	61	394	10 years, stop 1 year	Metastatic undifferentiated NSCC of lung	Nephroangiosclerosis
6.	C	M	35	256	2 years	Intra alveolar haemorrhage with parietoalveolar damages	No lesion
7.	C	F	43	36	No	Massive acute bronchopneumonia with abscess formation and necrosis	ATN, mesangiosclerosis without deposits (κ/λ/IgA/IgG/EM)
8.	C	M	83	488	6 years	Acute bronchopneumonia with abscess formation	Nephroangiosclerosis
9.	C	F	43	535	Ukw	Acute bronchopneumonia with focal abscess formation	Mesangiosclerosis, without deposits (κ/λ/IgA/IgG)
10.	WA	M	27	Ukw	Ukw	Systemic tuberculosis	Mesangiosclerosis, without deposits (κ/λ/IgA/IgG)
11.	SA	M	34	337	Yes	Peripherical thromboembolism and ARDS	No lesion
12.	C	M	63	Ukw	No	Ascendant aortic tear with haemopericardium	Nephroangiosclerosis
13.	C	M	38	1	No	Congestive heart failure	Mesangiosclerosis without deposits (κ/λ/IgA/IgG/EM)
14.	C	M	44	93	2 years	Acute pyelonephritis with abscess formation and organizing bronchopneumonia with abscess formation	Acute pyelonephritis
15.	C	F	49	73	Yes	Upper digestive haemorrhage	Diabetic mesangiosclerosis
16.	C	M	62	112	Yes	DAD, bronchopneumonia and blastic myelodysplasic syndrome	Mesangiosclerosis, without deposits (κ/λ/IgA/IgG)
17.	C	M	49	Ukw	Ukw	Acute pulmonary oedema	ATN
18.	C	M	39	199	Yes	DAD	ATN
19.	C	M	43	559	Yes	Arrhythmia	Malignant nephroangiosclerosis

[a]ANT, the Netherlands Antilles; ARDS, Acute Respiratory Distress Syndrome; ATN, Acute Tubular Necrosis; C, Caucasian; DAD, Diffuse alveolar damage; EM, electron microscopy; NSCC, non-small-cell carcinoma; SA, South America; Ukw, Unknown; WA, West Africa.

immune system [14]. Thus, several B-cell subpopulations, which are normally not present to any substantial degree in the peripheral blood of uninfected individuals, can make up considerable fractions of the total B-cell population in HIV patients. These include immature transitional B cells, exhausted B cells, activated mature B cells and plasmablasts. B-cell hyperactivation by HIV is characterized by hypergammaglobulinemia, increased polyclonal B-cell activation, cell turnover, differentiation to plasmablasts, production of auto-antibodies and increased frequency of B-cell malignancies. Therefore, B-cell dysregulation, in the context of impaired T-cell responses as well as an altered cytokine milieu, could contribute a clonal expansion. It is noteworthy that many of the B-cell abnormalities can be reversed by an antiretroviral therapy.

In conclusion, renal LCDD is rarely observed in HIV patients. The case we reported here was diagnosed at autopsy in a severely immunodepressed patient. The severe and peculiar immunological conditions of our 'treatment-naive' patient, reflected by the dramatic decrease of the CD4 cell count (24/μL), might therefore have played a role in the renal disease.

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Conflict of interest statement. None declared.

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