CASE REPORT

Clinical challenges of an oligosecretory plasma cell dyscrasia

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SUMMARY

Light chain deposition disease (LCDD) and immunoglobulin light chain (AL) amyloidosis are uncommon, and heterogeneous clonal plasma cell (PC) proliferative disorders defined by the different biochemical characteristics of the underlying anomalous immunoglobulin. The deposits are usually multisystemic and the two diseases can coexist. The diagnosis is sometimes made difficult by the absence of a detectable paraprotein by routine immunofixation techniques, and the use of serum-free light chain (FLC) immunoassay brought new value in terms of their diagnosis, prognosis and assessment of treatment response. Association of LCDD and AL amyloidosis with multiple myeloma (MM) at the time of diagnosis is common, but further progression to this condition is considered rare. We present a case of a patient diagnosed with systemic LCDD and AL amyloidosis of atypical biochemical characteristics, with no paraprotein detected in immunoelectrophoresis and immunofixation techniques, who progressed to MM in the later course of her disease.

BACKGROUND

Plasma cell (PC) dyscrasias are a group of clinically and biochemically distinct systemic disorders, characterised by the disproportionate proliferation of one or more clones of PC and the presence of an identical (monoclonal) immunoglobulin in the serum or urine. In light chain deposition disease (LCDD) and light chain (AL) amyloidosis light chains are the immunoglobulin subunits that precipitate in tissues being responsible for the pathological manifestations. The unique structural heterogeneity of this precursor enables the coexistence of both fibrillar and granular light chain deposits.¹ In approximately 10% of the LCDD and AL amyloidosis patients, the absence of a detectable paraprotein by routine immunofixation techniques makes the diagnosis challenging.^{2–3} Finding this paraprotein is clearly the diagnostic hallmark of the disease and permits an early diagnosis and prompt beginning of the treatment preventing substantial involvement of parenchymal organs. The serum immunoglobulin-free light chain (FLC) assay brought new value for the diagnosis, prognosis and assessment of treatment response in these PC dyscrasias. Its integration in international diagnostic and treatment guidelines is ongoing.^{4–7} Combination of immunochemical techniques and the FLC assay detects an abnormal result in 99% of patients.³ A recent paper reported that the serum FLC ratio was abnormal in all of their monoclonal immunoglobulin deposition disease patients, and

only less than three-quarters (73%) had an M-spike in the serum protein electrophoresis.⁸ Multiple myeloma (MM) is the most commonly associated lymphoproliferative disorder with both LCDD and AL amyloidosis. These are often the presenting disease leading to an early stage myeloma diagnosis. Delayed progression to overt myeloma of LCDD and amyloidosis AL patients that lack this diagnosis is, however, rare.^{9–10}

CASE PRESENTATION

A 44-year-old Caucasian woman was referred to our nephrology department by her assistant physician owing to chronic renal insufficiency of unknown aetiology (serum creatine (SCr) 1.8 mg/dl 5 months before admission) and nephrotic range proteinuria (3.7 g/24 h) with normoalbuminaemia. Her medical history included uncontrolled hypertension diagnosed 7 years earlier, impaired glucose tolerance, hypothyroidism, early onset of menopause (at the age of 42), tobacco consumption (30 cigarettes/day since the age of 15–40 smoking pack years) and two normal pregnancies. At presentation, the patient's symptoms were generalised weakness and weight loss (14 kg during the past year). Her family medical history included prostatic cancer leading to her father's death and her mother's death owing to a cerebrovascular accident. Physical examination revealed a good performance status (Karnofsky Performance Status Scale of 90%), with apparent age slightly superior to the real age, a body mass index of 23.5 kg/m² and a high blood pressure (150/100 mm Hg). Her neurological, cardiac, pulmonary and abdominal examinations were normal. She had slight pitting oedema on both of her ankles. Laboratory results at admission were as follows: haemoglobin 12.7 g/dl (normal range 11.9–15.5 g/dl), white blood cell count $7.7 \times 10^9/l$ (normal range $3.8–10.5 \times 10^9/l$), erythrocyte sedimentation rate 87 mm/h (normal range 0–20 mm/h), SCr 1.8 mg/dl (normal range 0.55–1.02 mg/dl), blood urea nitrogen 40 mg/dl (normal range 7.94–20.9 mg/dl), normal serum electrolytes, albumin 4.2 g/dl (normal range 3.5–5.2 g/dl), total cholesterol 299 mg/dl, HDL cholesterol 48 mg/dl, low-density lipoprotein cholesterol 238 mg/dl, triglycerides 226 mg/dl, alkaline phosphatase 169 U/l (normal range 30–120 U/l), γ -glutamyl transpeptidase 62 U/l (normal range <38 U/l) and a 24 h urine protein of 3712 mg. Her abdominal ultrasonography was normal and her renal ultrasonography revealed normal-sized kidneys with increased parenchymal echogenicity and some loss of corticomedullary differentiation. She was prescribed with an ACE

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inhibitor and an angiotensin receptor blocker (ARB), and a complete study for the renal disease was performed. Her additional diagnostic tests included a serum protein electrophoresis (SPE) that showed hypogammaglobulinaemia. All immunoglobulin levels were low: IgG 4.24 g/l (normal range 7–16 g/l), IgA 0.42 g/l (normal range 0.7–4 g/l), IgM 0.20 g/l (normal range 0.4–2.3 g/l), κ light chain 3.10 g/l (normal range 6.6–14.6 g/l), λ light chains 2.02 g/l (normal range 2.9–6.9 g/l) and a normal κ/λ relation 1.53 (normal range 1.35–2.65). Serum and 24 h urinary immunofixation were negative for a monoclonal gammopathy. Her C3 and C4 levels, rheumatoid factor, antistreptolysin-titre, antinuclear antibodies, antineutrophil cytoplasmic antibodies, cryoglobulins and glomerular basement membrane antibodies were within the reference values. The viral serology showed negative hepatitis B surface antigen, negative hepatitis B surface antibody, negative hepatitis B core antibody, negative hepatitis C antibody and negative HIV 1 and 2 antibodies. Her estimated creatine clearance, using the IDMS-traceable MDRD formula (modification of diet in renal disease—glomerular filtration rate (GFR) (ml/min/1.73 m²) = $175 \times (S_{cr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742, \text{ if female}) \times (1.212, \text{ if African-American})$ (conventional units)), was 31 ml/min/1.73 m².

Over her next appointments, she maintained high blood pressure and nephrotic range proteinuria. Four antihypertensive drug classes, with drugs at maximum dosage, were needed for optimal blood pressure control. A study for secondary causes of hypertension was negative. A renal biopsy was not performed owing to the advanced renal impairment at presentation, her history of uncontrolled high blood pressure and the patient's apprehension to do so. Progressive deterioration of renal function was observed and 11 months after the initial consultation, her SCr was 4.6 mg/dl. She maintained good diuresis, and after being presented with the different available renal replacement therapies, the patient chose peritoneal dialysis. She initiated continuous ambulatory peritoneal dialysis (CAPD) approximately 1 year after our first observation with a presumed diagnosis of hypertensive nephroangiosclerosis.

A few months after initiating dialysis, the patient's blood pressure dropped rapidly to below normal values. All antihypertensive agents were withdrawn, although the patient frequently presented recurrent orthostatic hypotensive episodes. By that time, she was transferred from CAPD to automated peritoneal dialysis owing to fast peritoneal transport status. Her glucose intolerance progressed to a diabetes mellitus and insulin treatment was required shortly thereafter. Her routine liver biochemistry also displayed variations and persistently abnormal values were found with a cholestatic pattern (γ -glutamyl transpeptidase and alkaline phosphatase 10 times superior to the reference range), normal bilirubin and a slightly increased INR (international normalised prothrombin ratio)—1.5. The abdominal ultrasonography showed an enlarged liver, with a regular shape and structure and a normal biliary tract. Other causes of hepatic disease were excluded and, with the patient's agreement, a transjugular liver biopsy was performed. Six portal spaces were visualised, displaying an inflammatory infiltrate of mononuclear cells. A loss of lobular organisation owing to the deposition of perisinusoidal eosinophilic amorphous material was present, conditioning some areas of trabecular collapse and hepatocanicular cholestasis (figure 1). This material had an affinity for periodic acid Schiff (figure 2) and stained with Congo red (figure 3) exhibiting dubious apple-green birefringence with polarised light. Immunohistochemical staining was positive for serum amyloid P and κ light chains (figure 4). Stains for serum amyloid A and λ light chain were negative. Owing to the combination of histological and immunohistochemical characteristics, the

Figure 1 H&E (magnification $\times 100$)—loss of lobular organisation owing to the deposition of perisinusoidal eosinophilic amorphous material, conditioning areas of trabecular collapse and hepatocanicular cholestasis.

histopathological diagnosis was a κ -LCDD and an AL amyloidosis. A skin biopsy was also performed, but insufficient tissue was collected. Bone marrow aspirate cytology showed 7% PC, and immunophenotyping detected two populations of these cells, 5% were phenotypically normal, with the remaining 95% positive for CD38, CD56 and presenting intracytoplasmic κ light chains. Metastatic skeletal radiological assessment was negative. A bone scintigraphy with 19 mCi HDP-Tc99m showed increased uptake on dorsal vertebrae 5 and 9 and the liver, suggesting metastatic bone disease and malignant hepatic disease.

The patient was started on prednisone and cyclophosphamide intravenous pulses, with a total of six performed. Clinical response was monitored and hypogammaglobulinaemia was constantly found in electrophoretic techniques. κ light chain remained within the normal range. The free light chain assay was not available at our institution at that time. The patient also performed serial F18-fluorodeoxyglucose positron emission tomography (FDG-PET) studies that never showed signs of active metabolic disease. Cytological analysis of bone marrow to assess treatment response was also performed on two other occasions with 9% PC 12 months after treatment was started, and 12% at 24 months, complying with the necessary criteria for the diagnosis of MM.

Her clinical condition slowly deteriorated with the need for recurrent hospital admissions. She presented three peritoneal dialysis-related peritonitis, one exit site infection and one deep

Figure 2 Periodic acid Schiff stain (PAS) (magnification $\times 200$)—material affinity for PAS.

Figure 3 Congo red (magnification ×400)—extracellular deposition of Congo red-positive amorphous proteinaceous material.

tunnel infection requiring peritoneal dialysis discontinuation and institution of haemodialysis for 1 month. Two years after she initiated CAPD, she presented clinical signs of congestive heart failure with episodes of orthopnoea and elevated brain natriuretic peptide. By that time, her echocardiogram showed a slight enlargement of the left atrium and an interventricular septal hypertrophy with a left ventricle ejection fraction of 45%. Refractory hypotension, progressive weight loss and muscular wasting were also noticed in periodic consultations. This patient died during a hospital admission with a septic shock owing to a Methicillin-resistant *Staphylococcus aureus*, isolated from the tip culture of a jugular central venous catheter, 39 months after the LCDD and AL amyloidosis diagnosis was made.

DISCUSSION

We have presented a case of a patient with the rare combination of LCDD and AL amyloidosis with renal and liver involvement and absence of a detectable paraprotein by immunoelectrophoresis and immunofixation techniques. These diseases result from a PC dyscrasia that produces a monoclonal immunoglobulin with atypical biochemical characteristics, enabling the development of fibrillar and granular light chain deposits. The potential of these light chains to precipitate in tissues and form different deposits is believed to depend on many factors, including molecular-mass, structural features in the light chain variable domain, glycosylation processing pathways and local environment.^{11–14} The fibrils in AL amyloidosis are derived from the

Figure 4 Immunohistochemical staining (magnification ×400)—positive for serum amyloid P and κ light chains (κ immunohistochemical staining shown).

variable region of λ light chains in approximately 70% of cases. In comparison to AL amyloidosis, the tissue deposits in LCDD are almost always composed of κ light chains.

Renal impairment was one of the first clinical signs of disease, confirming that the kidney, owing to its unique anatomophysiological characteristics, is the organ most commonly involved. Nephrotic range proteinuria, with or without renal insufficiency, is frequently present in both diseases and the progression to end-stage renal disease is known, despite therapy.^{15 16} A renal biopsy at the time of presentation was of significant value and light microscopy and immunohistochemistry analysis would reveal the type of renal involvement. Electron microscopy is, however, the definitive tool to show the fibrillar deposits typical of amyloid and the classic finely granular deposits of LCDD. The diagnosis of a PC dyscrasia is highly dependent on the finding of a detectable paraprotein in serum or urine and, in approximately 10% of patients, it is impossible with routine immunofixation techniques.^{2 3 15} The hypogammaglobulinaemia found in SPE could also point to a monoclonal cell dyscrasia. Panhypogammaglobulinaemia is seen in approximately 20% of patients with primary amyloidosis, often associated with a nephrotic pattern.²

Serum FLC immunoassay was not available at our hospital at that time, and could have been of great aid in reaching a diagnosis. The high sensibility of this test in oligosecretory disease has led to its incorporation in the diagnosis of PC dyscrasias and treatment guidelines.^{4–7 17}

This patient developed LCDD and AL amyloidosis at a younger age than expected. These diseases are not usually present before the sixth decade of life, although an earlier presentation has been seen in patients with pure monoclonal immunoglobulin deposition diseases.¹⁵

The choice of peritoneal dialysis for renal replacement therapy is accepted in AL amyloidosis and LCDD despite the more common use of haemodialysis in the published series.^{15 16 18 19} The hypothesis that orthostatic hypotension and progression to diabetes in this patient was related to light chain deposition in autonomic nervous system seems plausible. We also consider that the choice for peritoneal dialysis was beneficial for our patient, avoiding the haemodynamic aggression of haemodialysis treatment. Intradialytic hypotension has already been reported as a major problem in patients with AL amyloidosis.^{16 19} This patient's history of hypothyroidism and early menopause might resemble a similar pathophysiology to the endocrinopathies described in patients with POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes). The cause of these endocrinopathies is yet unknown but upregulated angiogenic factors are thought to play a role in its pathogenesis.^{20 21}

Monitoring treatment response in oligosecretory PC dyscrasias was more difficult before the use of the FLC assay and we experienced this difficulty. FDG-PET has been associated with false negatives in oligosecretory disease, especially in identifying small-sized lesions.²² Another explanation could be given by their small glycolytic activity, missing the necessary threshold for detection.

Late progression to MM ensued in the patient and overlapped the rapid decline of her quality of life in the last months. This progression is considered rare, but has already been reported in patients without serious cardiac or hepatic disease who have lived longer.¹⁰

Patient and renal survival rates are considered poor in LCDD and AL amyloidosis, but early detection and treatment can provide an increased benefit. It is promising to assume that

future understanding of mechanisms, and structural basics, of these light chain deposits will assure more effective treatment options.

Learning points

- ▶ Light chain deposition disease and immunoglobulin light chain amyloidosis are multisystemic deposit diseases that can coexist in the same patient.
- ▶ Finding a paraprotein is the diagnostic hallmark of these diseases and permits an early diagnosis and prompt beginning of treatment.
- ▶ The serum immunoglobulin free light chain assay brought new value for the diagnosis, prognosis and assessment of treatment response in oligosecretory PC dyscrasias.
- ▶ Progression to MM is possible in patients with extended survival.

Competing interests None.

Patient consent Obtained.

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