Lymphoplasmacytic lymphoma causing light chain cast nephropathy

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Abstract
Plasma cell dyscrasias are frequently associated with kidney disease through the production of monoclonal immunoglobulin but with a diverse set of pathologic renal patterns. While almost all patients with a renal biopsy showing a cast nephropathy have myeloma, kidney involvement associated with pathological immunoglobulin light chains and lymphoma is rare. To our knowledge, this is the first report of a cast nephropathy associated with lymphoplasmacytic lymphoma. We emphasize the relation between light chain deposition and renal dysfunction in this disease with production of light chains. A therapeutic approach that decreases light chain production appears to be warranted in these patients.

Keywords: acute renal failure; cast nephropathy; lymphoma; paraproteins

Background
Multiple myeloma is commonly associated with renal failure. A necropsy study of patients with myeloma demonstrated renal lesions in ~50% of the patients [1]. Almost all patients with a renal biopsy showing a cast nephropathy have multiple myeloma [2] but the association of cast nephropathy with lymphoma is exceptional [3, 4].

We present a patient with a lymphoplasmacytic lymphoma (LPL) and acute renal injury caused by cast nephropathy that illustrates the relation between light chain deposition and renal dysfunction but also represents a good example of the multiple causes of renal injury due to lymphoma that often present a diagnostic challenge for the nephrologists.

Case report
A 76-year-old woman was diagnosed in 2003 with systemic lupus erythematosus on the basis of mild arthritis and leucopenia; a homogeneous anti-nuclear antibody pattern was found on indirect immunofluorescence and the titre was 1:640, which was associated with the presence of anti-Sm, anti-La, anti-Ro and IgM anti-cardiolipin. Treatment with chloroquine and low-dose prednisone was started with a good clinical response.

In February 2009, the patient showed slow growing cervical lymphadenopathy and monoclonal gammopathy (IgM Kappa Isotype). Bone marrow biopsy revealed a diffuse infiltrate of 42% small lymphocytes and 6% plasma cells. Lymph node biopsy confirmed an LPL (Figure 1).

Because of the indolent course of the lymphoma and the clinical context, no specific therapy was initially given. Ten months later, due to progression of the lymphoproliferative syndrome with lymph node enlargement, treatment with rituximab was started. At the same time, a renal biopsy was performed because of proteinuria 2.4 g/24 h and progressive elevations in the plasma creatinine concentration from 0.90 to 2.3 mg/dL. The biopsy showed focal and segmental glomerulosclerosis, with no evidence of light chain deposits.

In July 2010, the patient was transferred to our department for evaluation of acute renal failure in the context of diarrhoea and vomiting during the previous 5 days. Physical examination showed dehydration, hepatomegaly, splenomegaly and palpable cervical adenopathy.

Laboratory tests showed serum creatinine 9.03 mg/dL, sodium 139 mEq/L, potassium 6.6 mEq/L, haemoglobin 7.3 g/L, total proteins were 60 g/L, albumin 26 g/dL, gamma globulins were 17.9% (IgM 17.7 g/L), calcium 7.1 mg/dL, erythrocyte sedimentation rate 120 mm/h and urine B-2 microglobulin 321.105 mcg/g. Microscopic urinalysis showed 1–3 red blood cells and 15 white blood cells per high power field. Proteinuria was 3 g/24 h and urine protein electrophoresis determined that 61.9% were gamma globulins, 7.5% alfa 1 globulins, 7.6% alfa 2 globulins, 18.7% beta globulins and 4.3% albumin. Serum immunofixation identified a monoclonal IgM kappa and IgG kappa, and urine immunofixation confirm the excretion of monoclonal kappa light chains (2.2 g/24 h).

The kidney biopsy showed evidence of light chain cast nephropathy (Figure 2).

A cast nephropathy associated with LPL was diagnosed and treatment with bortezomib, and dexamethasone, as well as 12 plasma exchange sessions, was instituted based on the experience with myeloma kidney.
Renal function improved with no dialysis support after 12 plasma exchange sessions (urine light chain levels were reduced to 1070 mg and serum creatinine to 3.11 mg/dL) but no haematological response was observed after two cycles of the selected induction therapy.

One week after plasma exchange recess, renal function again decreased to serum creatinine of 5.87 mg/dL, associated with an increase in urine IgM kappa chains. The induction therapy was switched to R-CHOP, followed by a further set of six plasma exchange sessions.

After this regimen, serum creatinine was reduced to 2.70 mg/dL with no dialysis requirement and urine kappa chains decreased to 1 g/L, with stabilization of renal function in the following weeks.

Discussion

This is an interesting case describing a patient with monoclonal gammopathy, not due to multiple myeloma, who develops cast nephropathy in the course of dehydration due to diarrhoea. The association of light chain cast nephropathy (LCCN) with lymphoproliferative disorders is quite rare; Waldenström’s macroglobulinaemia (WM) is defined as LPL with bone marrow involvement and monoclonal gammopathy but with normal lymph node architecture [5] and only one associated case of LCCN has been reported in a patient with WM [3]. To our knowledge, this is the first report of cast nephropathy associated with LPL with bone marrow and lymph node infiltration.

Moreover, her first kidney biopsy specimen showed other distinctive pathologic findings associated with lymphoma: focal segmental glomerulosclerosis (FSGS). Kidney involvement in lymphoma is a well-recognized phenomenon, but the presence of several distinct pathologic processes is rarely seen. Because biopsy is performed infrequently in patients with lymphoma, it is likely that cases with multiple forms of kidney involvement are overlooked.

Lymphoma-associated kidney involvement occurs by a variety of mechanisms, which differ in prevalence and clinical presentation. In post-mortem studies, lymphomatous infiltration is found in 34% of these patients but only 14% had been diagnosed before death [6].

Paraneoplastic glomerulonephritis can happen in association with lymphoma. The most frequent cause of nephrotic syndrome is minimal-change disease associated with
Hodgkin lymphoma [7] but cases of FSGS and membranous glomerulopathy have been related to other lymphomas; specifically FSGS has been reported in seven patients with Hodgkin lymphoma and four patients with non-Hodgkin lymphoma and is considered by some to represent a later stage of kidney damage caused by a soluble permeability factor, unidentified to date, that causes loss of selective capillary permeability and allows albumin and other negatively charged molecules to cross the glomerular barrier [8, 9].

Kidney involvement associated with immunoglobulin light chains and lymphoma is exceptional, but cases of monoclonal immunoglobulin glomerular deposition disease [10], amyloidosis [11] and immunotactoid glomerulopathy [12] as a cause of proteinuria and renal dysfunction in patients with lymphoma have been described.

Figure 3 provides a comprehensive description of lesions seen in patients with lymphoma and renal manifestations; it summarizes the number of published case reports and series with corresponding histological diagnosis [7, 13–15] and puts the prevalence of paraneoplastic glomerulonephritis in low, although MCD is the most common histological pattern in LH and MPGN in LNH. Abbreviations: LH, lymphoma hodgkin; LNH, lymphoma non-hodgkin; MCD, minimal change disease; IGA, IgA nephropathy; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis; AM, amyloidosis; INGN, immunotactoid glomerulonephritis; CRGN, crescentic glomerulonephritis.

Figure 3. Lesions seen in patients with lymphoma and renal manifestations. Number of cases is reported in the left of the figure. The prevalence of paraneoplastic glomerulonephritis is low, although MCD is the most common histological pattern in LH and MPGN in LNH. Abbreviations: LH, lymphoma hodgkin; LNH, lymphoma non-hodgkin; MCD, minimal change disease; IGA, IgA nephropathy; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis; AM, amyloidosis; INGN, immunotactoid glomerulonephritis; CRGN, crescentic glomerulonephritis.

Conflict of interest statement. None declared.

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