Mixed cryoglobulinaemia not related to hepatitis C virus, mesangiocapillary glomerulonephritis and lymphoplasmocytic lymphoma

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ABSTRACT

Kidney involvement associated with lymphoma is a known phenomenon but is not frequently characterised due to the low frequency with which biopsies are performed in these patients. Several histological patterns can co-exist and go unnoticed without a biopsy. Renal parenchyma infiltration by lymphoma has been found in 34% (post-mortem) and 14% (pre-mortem) of cases, and has a low incidence of clinical manifestations. Other patterns of renal injury are associated with lymphoma, and minimal change disease is especially related to Hodgkin’s lymphoma. Renal lesions associated with paraprotein in lymphoplasmocytic lymphoma are a rare exception, in spite of the appearance of cryoglobulinemia in 20% of these patients. There are a few cases reported in the literature with different histological patterns: light-chain disease, amyloidosis, and immunotactoid glomerulopathy related to kidney injury in patients with lymphoma. A 39-year-old male presented with an association between paraproteinemia, non-hepatitis C virus-related membranoproliferative glomerulonephritis, and lymphoplasmocytic lymphoma with renal infiltration. This case emphasised the variety of renal lesions that lymphomas can trigger and the value of nephropathology in the diagnosis and outcome of the haematological diseases involving paraproteinemia.

Keywords: Cryoglobulinemia. Membranoproliferative glomerulonephritis. Lymphoplasmocitary lymphoma. Hepatitis C virus.

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the low frequency of biopsies performed in these patients, in which several different histological patterns may coexist and go unnoticed in the absence of a histopathological analysis.\(^1\)

Infiltration of the renal parenchyma by a lymphoma is not an uncommon phenomenon, and it has been observed in up to 34\% of cases in post mortem studies. However, only 14\% of these were actually diagnosed before death, due to the low incidence of clinical manifestations and/or renal failure observed in these patients. Additionally, several different studies have shown that lymphomatous infiltration of the kidney is associated with a poor prognosis from a haematological point of view.\(^1\)

However, there are other patterns of renal damage associated with lymphomas, such as the association of minimal-change disease with Hodgkin’s lymphoma, in which this glomerulopathy accounts for 40\% of all cases with renal disease.\(^1\) On the contrary, the association of membranoproliferative glomerulonephritis and lymphoma is much less frequent than the rate published for this glomerular disease with regard to solid organ tumours.\(^1\) Renal damage associated with paraproteins synthesised by lymphoplasmacytic lymphoma is a rare occurrence, despite the fact that approximately 20\% of lymphoplasmycatic lymphomas progress with cryoglobulinemia and the almost always present IgM kappa monoclonal gammopathy.\(^2\) Cases have been described in the medical literature of light-chain disease,\(^3\) amyloidosis,\(^7\) and immunotactoid glomerulonephritis\(^6\) as causes of proteinuria and renal failure in patients with lymphoma. Here, we present, in chronological order, an example of the association between the appearance of paraproteinaemia, membranoproliferative glomerulonephritis, and a clinically evident lymphoplasmycatic lymphoma (LPL) in the absence of infection by hepatitis C virus (HCV), which shows the polymorphic manifestations that lymphomas can take in the kidney, as well as the value of nephropathology in the diagnosis and prognosis of a haematological disease that presents with paraproteinaemia.

**CLINICAL CASE**

Our patient was a 39-year-old male, with no toxic habits, allergic to acetylsalicylic acid (ASA) and diclofenac. He initially sought treatment for swelling of the soft tissues associated with palpable purpura in the lower extremities in April 2001. We performed an immunological analysis that revealed positive cryoglobulinemia with a cryocrit of 9.2\% (monoclonal IgM kappa and IgG component). Serology tests for hepatotropic virus and human immunodeficiency virus (HIV) were negative, and the antiphospholipid antibody test was also negative.

A physical examination revealed the presence of palpable purpura in the lower extremities; the rest of the exam was normal. He underwent thoraco-abdominal computerised tomodiography (CT) that did not show any evidence of adenopathies or visceromegalies. Diagnosed with cutaneous vasculitis, the patient was prescribed prednisone at 1mg/kg/day, with favourable initial evolution and the disappearance of lesions.

One year after the first medical visit, the patient complained of paraesthesia in the lower extremities, again associated with petechiae in the same area, and on this occasion the patient also had nephritic syndrome. The laboratory analysis resulted in: hypocomplementemia, cryocrit of 17\%, and a proteinogram with a weak anomalous band in the gamma zone. The serum immunoelctrophoresis showed restricted mobility IgM kappa component (there was no evidence of monoclonality in the urine). Renal function included a creatinine level of 1.2mg/dl, sediments with +++ red blood cells, and proteinuria at 2.8g/day.

A kidney biopsy confirmed the presence of glomerulonephritis with a mesangiocapillary pattern (Figure 1). We added azathioprine to the treatment regimen, maintaining renal function and proteinuria close to 1g/day.

After 6 months of follow-up, a control laboratory test revealed an immunophenotype that was compatible with LPL in a peripheral blood sample. This finding was later confirmed through a bone marrow aspiration that revealed medullary infiltration from small-type B-cell chronic lymphoproliferative syndrome, compatible with quiescent LPL, and so at this point the patient was no longer given chemotherapy.

One year later, the patient developed persistent proteinuria (4.7g/24h), for which we took another renal biopsy that confirmed the presence of cryoglobulinemic glomerulonephritis, and also showed lymphocyte infiltration compatible with low-grade B-cell lymphoma (Figure 2). Given the renal involvement of the lymphoma, we decided to start treatment with subcutaneous rituximab at 375mg/m\(^2\)/day and a cycle of plasma exchange.

Two years after receiving anti-CD20 treatment, the patient currently has lymphoproliferative syndrome that is in remission, and the renal damage continues in the form of residual proteinuria (4g/day), with conserved renal function (Cr: 0.8mg/dl, GFR: 100ml/min) and treatment with dual blockade of the renin-angiotensin-aldosterone system (Figure 3).

**DISCUSSION**

In addition to the peculiar clinical progression of this patient, in which mixed cryoglobulinemia was the first manifestation of LPL, this case exemplifies the rare association between lymphoma and cryoglobulin-associated glomerulonephritis. The absence of HCV stands out, since it is common in pa-
In 10 cases (55%), there was a coexisting glomerular pathology: five had glomerulonephritis with membranoproliferative patterns (n=4) and membranous nephropathy (n=1), characterised by immune complex deposits; two had immunoglobulin deposition with a monoclonal component of amyloid lambda light chains (n=1), and light-chain deposition disease (n=1); two had minimal change disease, and one patient had focal pauci-immune crescentic glomerulonephritis. Additionally, one biopsy revealed diabetic nephropathy, and three cases had non-specific ischaemic changes. In the four remaining cases there were no significant glomerular changes. In 11 cases (61%), the diagnosis of lymphoproliferative syndrome was made after renal biopsy.

This case highlights the usefulness of renal biopsies as a diagnostic tool for: 1) better characterisation of the different stages of lymphomas with renal manifestations, since they can be polymorphic, as in our patient, who progressed from...
nephritic syndrome to nephrotic syndrome, and 2) as a biological substrate upon which to suggest an early treatment regimen for this type of haematological pathology.

CONCLUSIONS

The kidneys can be a target organ in patients with LPL. The early indication for renal biopsy in patients with renal damage and LPL will allow us to determine other rare patterns of renal damage that are produced in patients with this type of lymphoma, and thus avoid under-registering the association between nephropathy and LPL.

Additionally, renal biopsies in these patients will facilitate a rapid diagnosis and early start of chemotherapy, which is a key factor in the renal recovery of patients with oncohaematological diseases.

Based on these conclusions, the relevance of analysing renal function and the urine sediment in the follow-up of patients with lymphoma is highlighted, as well as cooperation with pathologists, allowing for a clinical-pathological partnership throughout the evolution of this disease.

REFERENCES