Primary renal MALT lymphoma presenting with cryoglobulinaemia

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Abstract
Primary renal lymphoma is a rare clinicopathologic entity that typically presents as renal mass or renal impairment with enlarged kidneys. We describe the case of a 66-year-old woman who presented with type II mixed cryoglobulinaemic vasculitis as the first manifestation of underlying low-grade primary renal lymphoma.

Keywords: MALT lymphoma; mixed cryoglobulinaemia; primary renal lymphoma

Introduction
Kidney involvement is not uncommon in systemic lymphoma, usually occurring in patients with disseminated disease [1, 2]. By contrast, primary renal lymphoma (PRL) is a very rare clinicopathologic entity, the kidney being one of the organs normally not containing lymphoid tissue [2]. There are few studies in the literature covering the topic of PRL. PRL typically presents as a renal mass or renal impairment in the setting of enlarged kidneys, and most cases are related to aggressive types of lymphoma [3]. Low-grade lymphomas represent exceptional aetiologies of PRL. We report here the case of a 66-year-old woman who presented with normal-sized kidneys, Type II cryoglobulinaemic vasculitis and acute kidney injury due to low-grade PRL. This is the first report of cryoglobulinaemia arising on the background of PRL.

Case
A 66-year-old woman was referred to the nephrology department due to deterioration of renal function found in laboratory tests that were carried out because of weakness, oedema, dyspnoea on exertion and hypertension for the last 4 months. Her medical history was unremarkable. On physical examination, blood pressure was 180/110 mmHg, temperature 36.6°C and pulse 82 beats per minute. There was 2+ pitting oedema in the ankles and palpable purpura on both legs. Laboratory examinations revealed a leukocyte count of 5370/μL, haemoglobin 10 g/dL, platelets 90 000/μL, erythrocyte sedimentation rate 102 mm/h, urea 152 mg/dL, creatinine 3.77 mg/dL, albumin 3.2 g/dL and lactate dehydrogenase 320 U/L. Liver function tests, electrolytes and C-reactive protein were normal. Urinalysis demonstrated 60 erythrocytes per high power field, granular and hyaline casts and nephrotic proteinuria (12 g/day). Ultrasonography showed kidneys of normal size, whereas Doppler examination did not reveal blood flow abnormalities. Computed tomography of head, chest and abdomen was unremarkable.

Immunoglobulin measurements showed IgG 501 mg/dL, kappa-free light chains 30.5 mg/L and lambda-free light chains 853 mg/L, lambda/kappa ratio 28.1. The patient’s serum tested positive for cryoglobulins and immunodiffusion of the cryoprecipitate demonstrated Type II mixed cryoglobulinaemia (MC). The cryocrit was 10% and the concentration of circulating immunocomplexes


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0.7 μg/L. Serological tests and polymerase chain reaction assays for hepatitis B, hepatitis C, and human immunodeficiency viruses were negative. The patient was IgM negative and IgG positive for Epstein–Barr virus and cytomegalovirus. Biopsy of a purpuric skin lesion revealed small-vessel leukocytoclastic vasculitis. Upper and lower gastrointestinal endoscopy and lower lip biopsy were normal. Gastric mucosal biopsies found no evidence of Helicobacter pylori infection. Bone marrow biopsy disclosed a reactive hypercellular marrow with no evidence of dysplasia or infiltration by a neoplastic process. Peripheral blood and bone marrow lymphocyte subsets were normal by flow cytometry. Since she had no symptoms or findings of peripheral neuropathy, nerve conduction studies for possible nerve involvement by MC were not performed.

Further investigation of MC in conjunction with nephrotic-range proteinuria prompted us to proceed to a diagnostic renal biopsy. Histologically, there was replacement of renal parenchyma by a dense lymphoid infiltrate composed predominantly of small and medium-sized lymphocytes with round or mildly irregular nuclear contours and moderate cytoplasm. Scattered plasma cells, monocytoid lymphocytes and a few immunoblasts were also observed. The neoplastic cells were CD45+, CD79a+, CD20+ and displayed monoclonal kappa light chain restriction (Figure 1). Immunostains for Tdt, CD3, CD5, CD23, CD10 and cyclinD1 were negative. Gene rearrangement studies confirmed the presence of a monoclonal B-cell population. The histopathological picture was consistent with B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) involving the kidney.

Therapy for lymphoma consisting of cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) and rituximab was commenced. Rituximab was given at a dose of 375 mg/m² on a weekly basis for the first 4 weeks and then administered with each CHOP cycle. The patient responded to treatment, and following four cycles of chemotherapy, her condition had improved substantially, vasculitic lesions had resolved, blood counts had recovered and serum creatinine was normal. Treatment was completed at eight cycles, after which proteinuria was 500 mg/24 h, RF and C4 had returned to normal, and cryoglobulins were not detected in serum. Three years post-treatment, the patient has normal renal function and no evidence of recurrent disease.

**Discussion**

PRL is a rare entity. It is defined as a non-Hodgkin’s lymphoma arising in the renal parenchyma in the absence of any extrarenal localization at the time of diagnosis or invasion from an adjacent lymphomatous mass [4]. The origin of PRL is incompletely understood because renal parenchyma normally does not contain lymphoid tissue. PRL usually affects middle-aged people and clinically manifests as a renal mass or as renal insufficiency with enlarged kidneys, bland urine sediment and notably an absence of significant proteinuria [2–4].

PRL is usually of B-cell lineage; most cases involve aggressive tumours such as diffuse large B-cell or Burkitt’s lymphoma [3]. Low-grade PRLs are very uncommon.
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MALT lymphoma is a low-grade B-cell neoplasm arising at extranodal sites, most frequently in the stomach, lung and salivary glands [5]. The kidney is a rare site of involvement, and only a handful of cases of primary renal MALT lymphoma have been reported [6]. MALT lymphomas are commonly preceded by chronic inflammation, e.g. gastric MALT lymphoma is usually associated with H. pylori gastritis. However, for renal MALT lymphomas, no specific predisposing condition has been identified [6]. Our patient underwent complete diagnostic work-up before it was decided that she had primary renal MALT lymphoma. Positron emission tomography scan was not selected as a staging procedure because its sensitivity is low in MALT lymphoma and therefore not recommended [7].

It should be noted that the patient’s clinical presentation did not indicate that renal parenchyma might be diffusely infiltrated by a malignant tumour. Uni- or bilateral kidney enlargement had been proposed in the past as one of the initial manifestations of MC. Cryoglobulins are serum proteins that precipitate at temperatures <37°C and dissolve on re-warming. They are either immunoglobulins or a mixture of immunoglobulins and complement [9]. Our patient had Type II MC signifying that cryoglobulin was comprised of monoclonal IgM and polyclonal immunoglobulin with RF properties. Most cases of MC are seen secondary to HCV infection or without an apparent underlying cause (‘essential’ MC); autoimmune (particularly Sjögren’s syndrome and lupus erythematosus) and lymphoproliferative disorders have also been implicated [9]. Regarding our patient, Sjögren’s syndrome contributing to MC and MALT lymphoma genesis was excluded by the absence of sicca symptoms and the negative results of lip biopsy and ENA antibodies.

Renal involvement is common in MC and is characterized by significant proteinuria, haematuria, hypertension, progressive renal failure and the finding of membranoproliferative glomerulonephritis with intra-luminal thrombi and sub-endothelial deposits in renal biopsies. Under electron microscopy (EM), affected glomeruli demonstrate dense sub-endothelial ‘fingerprint’-like deposits. Our patient displayed the clinical features of cryoglobulinaemic vasculitis with renal involvement; however, kidney biopsy revealed infiltration of the renal parenchyma by a low-grade PRL and not membranoproliferative glomerulonephritis as expected. As a result of the dense lymphomatous infiltration, no intact glomeruli were observed in the biopsy specimen to permit morphologic, immunohistochemical or EM glomerular studies. However, it is reasonable to presume that cryoglobulinaemic glomerulopathy co-existed with the lymphomatous process in other parts of the kidneys because the patient had nephrotic proteinuria and active urine sediment. If neoplastic kidney infiltration was the only cause for renal impairment, we would expect a different pattern of kidney disease with low-grade proteinuria.

MC is a rare manifestation of lymphoma and to our knowledge, it has not been correlated with renal lymphoma previously. The target of treatment in lymphoma-associated MC is the remission of lymphoma and the regression of clinical manifestations of MC. Of note, rituximab, which is standard treatment for B-cell lymphomas, also has a particular beneficial effect in MC [10, 11].

In this article, we report the unusual coexistence of primary renal MALT lymphoma and Type II MC. This case illustrates the significance of obtaining a diagnostic renal biopsy in patients with apparent essential MC nephropathy. The identification of renal lymphoma in our patient had a dramatic effect on the selection of appropriate treatment and the successful outcome.

Conflict of interest statement. None declared.

References


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