AJKD
Teaching Case

Membranous Nephropathy and Intrarenal Extramedullary Hematopoiesis in a Patient With Myelofibrosis

Carole Philipponnet, MD,[1,2] Pierre Ronco, MD, PhD,[3] Julien Aniort, MD,[1,2] Jean-Louis Kemeny, MD, PhD,[2,4] and Anne-Elisabeth Heng, MD, PhD[1,2]

Teaching Cases focus on interpretation of pathology findings, laboratory tests, or imaging studies to educate readers on the diagnosis or treatment of a clinical problem.

Kidney disease in the setting of a hematologic malignancy is common, with the frequency and type of kidney disease varying depending on the specific malignancy. Various glomerular diseases and tumor infiltration of the kidneys have been reported in patients with lymphoproliferative disorders. Descriptions of kidney involvement in myeloproliferative disorders have been much rarer. We report a case of membranous nephropathy accompanied by kidney injury in a patient with primary myelofibrosis with additional features considered related to the patient's myeloproliferative disorder. A 63-year-old patient with primary myelofibrosis underwent kidney biopsy to investigate nephrotic-range proteinuria and reduced kidney function. Histologic analysis revealed mesangial sclerosis and hypercellularity, changes indicative of membranous nephropathy, and infiltration of hematopoietic cells into the renal interstitium, peritubular capillaries, and perirenal tissue consistent with extramedullary hematopoiesis. He was treated with renin-angiotensin blockade and a Janus kinase inhibitor, resulting in improvement in kidney function and proteinuria.
Am J Kidney Dis. 70(6):874-877.

INDEX WORDS: Extramedullary hematopoiesis; glomerulonephritis; membranous nephropathy; myeloproliferative disorder; myelofibrosis; JAK inhibitor; acute kidney injury (AKI); proteinuria; nephrotic syndrome; case report; kidney biopsy.

INTRODUCTION

Kidney involvement in the setting of hematologic malignancy is common and varies greatly depending on the type of malignancy present. Tumor infiltration and various forms of glomerulopathy (podocytopathy with minimal change disease or focal segmental glomerulosclerosis, membranous nephropathy, or membranoproliferative glomerulonephritis) have been reported in both Hodgkin and non-Hodgkin lymphoproliferative disorders. Descriptions of kidney involvement in myeloproliferative disorders have been much rarer.

We report a case of membranous nephropathy in a patient with myelofibrosis. In addition to membranous nephropathy, there was glomerular sclerosis and mesangial hypercellularity with evidence of intrarenal extramedullary hematopoiesis related to the underlying myeloproliferative disorder.

CASE REPORT

Clinical History and Initial Laboratory Data

A 63-year-old man was admitted to the hospital with nephrotic syndrome, edema, and acute kidney injury (AKI). Urinary protein-creatinine ratio was 5.8 g/g, serum albumin concentration was 2.5 g/dL, and serum creatinine concentration was 210 μmol/L (from a baseline value of 105 μmol/L). There was no hematuria. He had a medical history of a Janus kinase (JAK) 2–negative myeloproliferative disorder discovered 30 years earlier when he was found to have thrombocytosis, splenomegaly, and a calreticulin exon 9 mutation. He was monitored without treatment until hydroxycarbamide was introduced 4 years before his most recent presentation due to worsening of thrombocytosis and anemia, requiring monthly red blood cell transfusions. Medications included nicardipine, allopurinol, aspirin, omeprazole, calcium carbonate, simvastatin, valsartan, furosemide, potassium chloride, hydroxycarbamide, and recombinant human erythropoietin.

Physical examination revealed edema and splenomegaly. The patient had anemia with a normal platelet count. Tests for antinuclear antibodies and antineutrophil cytoplasmic antibodies were negative, and complement levels (C3 and C4) were normal. There was no monoclonal gammopathy and viral serologic tests for hepatitis B and C viruses and human immunodeficiency virus (HIV) were negative. Tests for serum anti-PLA_2R antibodies were also negative.

From the [1]Nephrology, Dialysis and Transplantation Department, Clermont Ferrand University Hospital; [2]UFR Medecine, Clermont Ferrand; [3]Nephrology and Dialysis Department, APHP, Tenon University Hospital, Paris; and [4]Anatomy and Pathology Department, Clermont Ferrand University Hospital, Clermont Ferrand, France.

Received November 26, 2016. Accepted in revised form June 27, 2017. Originally published online August 16, 2017.

Address correspondence to Carole Philipponnet, MD, Nephrology, Dialysis and Transplantation Unit, Clermont Ferrand University Hospital, Clermont Ferrand, France. E-mail: cphilipponnet@chu-clermontferrand.fr

0272-6386
http://dx.doi.org/10.1053/j.ajkd.2017.06.022

Additional Investigations

To assess the cause of nephrotic syndrome and AKI, a kidney biopsy was performed (8 glomeruli; Fig 1). Light microscopy revealed a diffuse increase in mesangial matrix and cellularity. There was noticeable thickening of glomerular basement membranes, which contained numerous silver-positive spicules. The interstitium revealed an abundant infiltrate composed of megakaryocytes, erythroid cells, and white blood cells, the latter being predominantly lymphocytic. These cells were also found in peritubular capillaries and perirenal adipose tissue. There were no other apparent abnormalities in the vascular and tubular compartments.

On immunofluorescence microscopy, there was diffuse granular basement membrane staining for immunoglobulin G (IgG) and C3, as well as κ and λ light chains. Stains for IgA, IgM, and C1q gave negative results. Analysis of immunoglobulin subclasses showed a very clear IgG4 predominance; IgG1, -2, and -3 were less intense. Electron microscopy showed diffuse subepithelial nonorganized electron-dense deposits, but no mesangial deposits. There was neither endothelial cell swelling nor expansion of the lamina rara interna.

Diagnosis

A diagnosis of membranous nephropathy was made. This was accompanied by features of a glomerulopathy consisting of mesangial sclerosis and hypercellularity with intrarenal extramedullary hematopoiesis, which we attribute to the underlying myeloproliferative disorder. AKI was attributed to diffuse extramedullary hematopoiesis in the renal interstitium.

Clinical Follow-up

Due to hematologic progression and AKI, therapy with the JAK inhibitor ruxolitinib was initiated and hydroxycarbamide treatment was discontinued; angiotensin receptor antagonist treatment was maintained. With this regimen, we noted improvement at 6 months in serum albumin concentration (3.5 g/dL), urinary protein-creatinine ratio (2 g/g), and serum creatinine concentration (120 μmol/L); moreover, splenomegaly and transfusion requirements improved.

DISCUSSION

Glomerular involvement in the setting of myeloproliferative disorders, with or without extramedullary hematopoiesis, has rarely been reported. In one study, 11 patients with myeloproliferative disorders underwent kidney biopsy to investigate the cause of proteinuria or kidney failure.[1] In all these cases, the authors described glomerulosclerosis and mesangial hypercellularity. In addition, focal segmental glomerulosclerotic lesions were described in 8 patients and features of thrombotic microangiopathy were described in 9. A second study of renal histopathology in 8 patients with myeloproliferative disorders and nephrotic-range proteinuria found glomerulosclerosis and/or mesangial hypercellularity in all and focal and segmental glomerulosclerotic lesions in 6.[2] Similar glomerular lesions of mesangial hypercellularity and sclerosis were present in our patient.

Myeloproliferative disorders are caused by clonal expansion of hematopoietic progenitors due to genetic dysregulation. Such hematologic malignancies result in bone marrow–derived overproduction of platelet-derived growth factor and transforming growth factor β by megakaryocytes. In the kidneys, platelet-derived growth factor is a potent stimulus of mesangial cell proliferation and is known to induce extracellular matrix production by mesangial cells.[3] Transforming growth factor β induces features of mesangial sclerosis by increasing mesangial cell collagen and fibronectin synthesis and exerts proapoptotic effects on podocytes.[4] These findings suggest a possible association between the elevated cytokine serum levels observed in myeloproliferative disorders and the observed glomerular lesions.

The occurrence of extramedullary hematopoiesis in the kidney is rare but has been observed in several hematologic malignancies (myeloproliferative disorder, multiple myeloma, and myelodysplastic syndrome), as well as benign blood disorders such as thalassemia, sickle cell disease, and immune thrombocytopenic purpura. Extramedullary hematopoiesis in the kidney is most frequently associated with myelofibrosis-related splenomegaly, as in the current case. In an autopsy study involving 70 patients with myelofibrosis-related splenomegaly, 35% exhibited renal hematopoietic infiltration.[5] A retrospective study recently described 14 patients in whom extramedullary hematopoiesis involving the kidney was noted.[6] All patients had hematologic malignancies (primary myelofibrosis, n = 9; unspecified myeloproliferative disorder, n = 1; essential thrombocythemia, n = 1; polycythemia vera, n = 1; and multiple myeloma, n = 2). The histologic appearance reported in that study ranged from interstitial parenchymal infiltration (n = 12) to perirenal infiltration (n = 3) to mass-like tumor (n = 1).[6] Parenchymal and perirenal involvement were also present in our case.

Extramedullary hematopoiesis in the kidney may be confused with acute interstitial nephritis unless there is careful assessment of the cellular content of the infiltrate. Distinguishing the 3 hematopoietic lineages in hematologic malignancies is essential, particularly in the event of myeloproliferative disorders.

In the previous study reporting 14 patients with renal extramedullary hematopoiesis, concurrent glomerulopathy was found in 10 patients: focal segmental glomerulosclerosis in 3 patients, chronic microangiopathy in 5 patients, fibrillary glomerulonephritis in 3 patients, and diabetic nephropathy in 2 patients.[6] To our knowledge, only 1 other case of membranous nephropathy in the setting of a myeloproliferative disorder has been reported.[7] In that instance, a 49-year-old patient with myeloproliferative disorder and nephrotic syndrome underwent a kidney biopsy that showed both intrarenal extramedullary hematopoiesis and membranous nephropathy. The authors hypothesized that the glomerulopathy was probably secondary to the hematologic malignancy. In our case, the negative anti-PLA_2R serology and absence of glomerular PLA_2R staining (the PLA_2R staining appeared in a podocyte cytoplasmic