PGNMID in a patient with diabetes mellitus

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Abstract

Diabetic nephropathy is a well known complication of diabetes mellitus and the leader cause of end-stage renal disease worldwide. Nonetheless, other forms of renal involvement can occur in diabetic population. Since it has prognostic and therapeutic implications, differentiating non-diabetic renal disease from diabetic nephropathy is of great importance. We report an 80-year-old man with well-controlled type 2 diabetes mellitus and hypertension, who presented with rapid deterioration of renal function, nephrotic proteinuria, microscopic hematuria and leukocyturia. The atypical clinical presentation prompted us to perform a kidney biopsy. A diagnosis of proliferative glomerulonephritis with monoclonal immunoglobulin deposits (light chain only variant) was made, with however some chronic histological aspects which made us took a conservative therapeutic attitude. We emphasize that other causes of chronic proteinuric kidney disease should be considered in patients with type 2 diabetes mellitus, based on clinical suspicion, absence of other organ damage and mostly if an atypical presentation is seen. We review the spectrum of monoclonal gammopathies of renal significance, focusing on this rare and newly describe entity.

Keywords

Membranoproliferative glomerulonephritis, proliferative glomerulonephritis with monoclonal immunoglobulin deposits, monoclonal gammopathy of renal significance

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Introduction

Monoclonal gammopathy of renal significance (MGRS) refers to a heterogeneous group of renal diseases caused by a monoclonal immunoglobulin (Ig) secreted by a B-cell or plasma cell clone. They do not meet criteria for hematologic malignancies such as multiple myeloma, Waldenström's macroglobulinemia, chronic lymphocytic leukemia or lymphoma, but can be associated with high morbidity. Renal disease occurs through direct deposition of Ig or its fragments, or by deregulation of the complement system.^{1,2} The first group can be caused by organized deposits, as in the case of Ig related amyloidosis or fibrillar, immunotactoid and type I or II cryoglobulinemic glomerulonephritis (GN); or due to non-organized deposits such in monoclonal Ig deposition disease and proliferative GN with monoclonal Ig deposits (PGNMID).^{2,3} PGNMID is a recently described, uncommon, kidney limited entity. Presenting features are non-specific and the monoclonal clone rate detection is considerably low.^{4–6} Histological findings are heterogeneous

but membranoproliferative GN (MPGN) pattern predominate. As it mimics other immunocomplex mediated GN, monoclonal staining of the deposits on immunofluorescence (IF) microscopy defines the diagnosis.⁷ The management of PGNMID remains unclear as the absence of a detectable clone in most cases difficult the choice of therapy. The renal prognosis is poor.^{4,8}

Case report

An 80-year-old white male was referred by his primary care physician to our evaluation for renal dysfunction with

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2 years of evolution (serum creatinine (sCr) of 2.3 mg/dL, urea (sU) of 87 mg/dL) and severely increased albuminuria (3.5 g/ day). His past medical history was remarkable for type-2 diabetes mellitus (DM) diagnosed 7 years before, without retinal involvement and well controlled with a single oral agent (glycated hemoglobin of 6.1%); arterial hypertension for more than 20 years, unsatisfactorily treated until a year ago; cerebrovascular disease with transient ischemic attack and cardiac pacemaker implantation for complete atrioventricular block both in 2018; dyslipidemia; overweight and past smoking habits. He was treated with azilsartan, chlorthalidone, furosemide, nifedipine, gliclazide, aspirin, bisoprolol and atorvastatin. Analysing his previous records we found out a normal renal function in 2016 (sCr 1.04 mg/ dL without active urinary sediment or proteinuria); with further deterioration in the following 2 years, despite clinical, metabolic and hemodynamic control. In August of 2018 he had sCr of 1.38 mg/ dL and albuminuria of 2.3 g progressing to sCr of 2.06 mg/dL, microscopic hematuria, leukocyturia and red blood cell and hyaline-cylindruria on the last month of that year.

The patient first presented to us in July of 2019 and besides peripheral oedema and hypertension (160/90 mmHg), physical examination was unremarkable, and he was asymptomatic. Key laboratory findings showed decreased renal function (SCr of 2.9 mg/dL, urea of 113 mg/dL, GFR 19.5 mL/min/1.73 m² according to CKD-EPI formula); abnormal urinalysis with microscopic hematuria (124 u/L), leukocyturia (25 u/L) and proteinuria (300 mg/dL); protein-creatinine ratio of 6.4 g/g and anemia (hemoglobin 10.1 g/dL, without hematinic deficiencies). Serum albumin (3.8 g/dL), serum protein electrophoresis and complement compounds (C3 and C4) were all normal and anti-glomerular basement membrane antibodies and anti-neutrophil cytoplasmic antibodies were negative. Hepatitis B surface antigen, anti-hepatitis C virus and anti-HIV 1/2 antibodies were also negative.

A kidney biopsy was performed. A total of 15 glomeruli were obtained. Under light microscopy, glomeruli appeared hyperlobulated and with mesangial expansion. There was also endocapillary hypercellularity; thickening of the capillary wall and double contour formation. The remaining four glomeruli were globally sclerosed. The tubulointerstitial compartment showed fibrosis and atrophy involving about 80% of the biopsy fragment (Figure 1), while the blood vessels were normal. Congo red staining for amyloid was negative. Direct IF examination of frozen renal tissue demonstrated granular glomerular capillary wall and mesangial deposits positive for Lambda + + +, C1q and C3 (Figure 2). There was no significant staining observed for IgG, IgM, IgA, and Kappa. Electron microscopy (EM) showed subendothelial electron dense deposits (Figure 3). These findings were consistent with MPGN due to lambda light chain paraprotein, thus leading to additional studies. Serum and urine protein electrophoresis did not suggest a monoclonal protein and serum immunoglobulin quantification and free light chain ratio

Figure 1. (a) Periodic acid–Schiff. Glomeruli appeared hyperlobulated, with mesangial expansion and endocapillary hypercellularity, (b) Methenamine Silver. Glomeruli has a membranoproliferative pattern with double contour formation, endocapillary and mesangial hypercellularity, and (c) Masson's trichrome. Tubulointerstitial compartment has extensive fibrosis and tubular atrophy.

were normal. Immunofixation electrophoresis showed a faint band of IgG Kappa and of Lambda light chain (LC), both unspecific. β 2-microglobulin was elevated (9.6 mg/mL, normal range 0.97–2.64 mg/mL) but there was no evidence of osteolytic lesions on skeletal radiography. Serological testing for cryoglobulins was negative. Bone marrow biopsy showed 2% of CD138 positive plasma cells; without lymphoma infiltration. No diagnostic criteria of hematological malignancy disorder were met. Considering clinical, histological and blood findings, the final diagnosis of PGNMID was made. After discussion with Hematology, taking into account all the pros and cons of chemotherapy in our patient, and given the degree

Figure 2. Immunofluorescence. There are granular deposits in the mesangium and capillary wall of lambda, C3 and C1q. Kappa is negative.

Figure 3. Electron microscopy showing subendothelial non-organized deposits ($\times 7000$).

of interstitial fibrosis and tubular atrophy, a conservative management of hypertension, metabolic control, chronic kidney disease (CKD) comorbidities and its risks factors was decided. After 1 year of follow-up, the patient remains clinical stable but a progressive loss of his renal function has been noted (sCr 4.78 mg/dL, sU 164 mg/dL, GFR 10.6 mL/min/1.73 m²). Accordingly, initiation of renal replacement therapy is being prepared.

Discussion

Diabetic nephropathy (DN) is a well known complication of DM and the leader cause of end-stage renal disease (ESRD) in the developed world. As a result, most renal

abnormalities in diabetic population are primarily attributed to it, frequently without further investigation of other etiologic culprits. However non-DN, either alone or superimposed to DN, should always be considered, especially when the renal dysfunction does not have a progressive course over the time or it is associated with atypical presentation.⁹ In our patient the rapid deterioration of kidney function in the absence of other organ involvement, the sudden increase in proteinuria and the presence of an active urinary sediment made us question, rendered DN less likely and led us to performed a kidney biopsy.

MPGN describes a glomerular-injury pattern common to a heterogeneous group of diseases that is further classified based on IF staining and pathophysiological process. It can be mediated by deposition of complement or Ig that can be polyclonal or monoclonal. This approach may facilitate proper diagnosis and treatment.^{8,10}

PGNMID is a recently described entity among the spectrum of MGRS diseases that is characterized by unorganized glomerular deposition of an intact monoclonal Ig. It is a rare disorder—biopsy incidence ranges from 0.17% to 3.7%, most commonly described in caucasians within the sixth decade of life.^{4,5,11} As there is no reports of extrarenal involvement, PGNMID is thought to be a kidney-limited disease.^{4,6,11} Renal presentation is non-specific and of variable severity. Proteinuria, usually in nephrotic range, is a constant. The majority of patients also present with hematuria or renal insufficiency, such as our patient did. Rapidly

progressive GN is uncommon and only a minority (<10%) require dialysis at the time of diagnosis.^{4,5} Similarly, described histological findings under optical microscopy are heterogenous. GNMP, as we present, is found in two thirds of the cases and is the most common pattern, followed by endocapillary proliferative GN, pure mesangial proliferative GN and membranous GN.⁴ IF defines the diagnosis as it shows irregular, coarsely granular deposits restricted to the glomeruli, localized to the mesangium and glomerular capillary wall. Monoclonal Ig, usually IgG, with a heavy chain subclass restriction (IgG3 in 60% of the cases) and a single LC isotope (Kappa in 73%) is most commonly involved. Variants with monotypic deposits of IgA, IgM or LC alone, as we found in our case, are extremely rare, accounting for less than 10% of the reports.^{4,5,7,12} Moreover, in the recently and first published series of 17 patients with LC-only variant PGNMID, only a minority of the cohort (29%) presented sole positivity for lambda LC.¹² Thus, for those without a heavy chain on biopsy, the finding of lambda only deposits, as presented by us, is of exception, placing our patient on a scarce group of patients with lambda LC-only variant PGNMID. Glomerular codeposition of C3 is typical and C1q can be present. On EM granular electron-dense deposits are confined to the glomerular compartment, primarily in the mesangium and subendothelial space, mimicking other immune-complex GN.^{4,5,7,12}

Despite the monoclonality on histology, in contrast to many of the other MGRS, only a minority of PGNMID patients will have detectable paraproteinemia or underlying B- or plasma cell clone (20–30%).^{4,6} An exception to this rule was recently described exactly for those with PGNMID-LC only variant, who, again as opposed to what we present, had a higher detection rate of the pathogenic clone comparing to PGNMID-IgG patients.¹² Since most patients with PGNMID have no overt malignancy, specific treatment remains to be established. If there is an identified M protein the current strategy is extrapolated from the other MGRS, and it relies on chemotherapy aiming the suppression of the clone.^{6,13} It includes bortezomib based regimens for those with IgG, IgA or LC-alone monoclonal gammopathy or anti-CD20 based regimens for those with an IgM driven disease. The decision to aggressively treat M-spike negative patients is more controversial but, when assumed, should be directed to the (hypothetically) monoclonal Ig-producing clone.^{4,13} The kidney response is related to the haematological course, but it is dependent on factors such as age, coexisting CKD and severity of glomerular fibrosis and tubulointerstitial atrophy. Thus the indication of chemotherapy should be carefully discussed in an individualized risk/benefit approach. In patients with stable CKD (stages 1 and 2) and without nephrotic syndrome renin-angiotensin-system blockade alone can be a reasonable strategy. In those with CKD Stage 5 who are not candidates for renal transplantation chemotherapy should not be used.⁴ Hereupon, in the absence of an overt

haematological malignancy and facing chronic histological findings and patient's frailty, we decided for a non-chemotherapeutic approach after discussion with Hematology. Overall, the PGNMID renal prognosis is poor. Among 32 treated patients with a mean follow up of 30 months, 22% progressed to ESRD, 38% showed continuous worsening of kidney function and only 13% presented complete recovery. Recurrence after kidney transplant is common, occurs early and is also associated with a bad allograft prognosis.^{4,11}

With this clinical report we emphasize the importance of clinical and complementary integration on the diagnosis of ND kidney disease in diabetic patients. Attention should be paid whenever an atypical course is present. We also highlight the rarity and the diagnostic and therapeutic complexity of PGNMID lambda LC only variety, an entity of recent and in description. As a new disease, specific data of PGNMID on diabetic patients is still lacking.

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