

Nephrotic syndrome secondary to amyloidosis in a patient with monoclonal gammopathy with renal significance (MGRS)

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Abstract

Monoclonal gammopathy with renal significance (MGRS) is a relative new-described entity, diagnosed especially in older patients and deriving from the group with monoclonal gammopathy of undetermined significance (MGUS). Various renal lesions may arise in MGRS, according to the ultrastructural characteristics of the monoclonal immunoglobulin deposition in the kidney, from proliferative glomerulopathies and amyloidosis to light chain proximal tubulopathy and crystal-storing histiocytosis. Although both are considered premalign or non-malignant hematological conditions, kidney involvement in MGRS aggravates the prognosis of the patients and need to be treated aggressively. We discuss the case of a 44-year-old female patient admitted in our Department of Nephrology for clinical picture of impure nephrotic syndrome and decreased renal function associated with Bence-Jones proteinuria. Renal biopsy was performed, and fibrillar amyloid deposits were demonstrated both in glomerular and tubular basement membranes; the immunofluorescence identified the presence of κ chains. Bone marrow aspiration and biopsy showed <10% plasmocytic proliferation confirming the diagnosis of MGRS.

Keywords: monoclonal gammopathy, nephrotic syndrome, renal biopsy, amyloidosis.

Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is a clinical asymptomatic disorder characterized by <3 g/dL monoclonal protein concentration in serum, <10% monoclonal plasma cells infiltration of the bone marrow, and by the absence of organ injury (*i.e.*, lytic bone lesions, anemia, hypercalcemia, renal insufficiency, hyperviscosity) encountered in multiple myeloma or other monoclonal gammopathies [1, 2]. Initially described by Waldenström more than 50 years ago and considered a benign monoclonal plasma cells proliferation [3], presently MGUS is recognized as having low potential of evolving into multiple myeloma, amyloidosis with light chain deposits or other related disorder, depending on the type of protein involved: non-IgM, IgM, light chain [4–6]. The pathophysiology of renal involvement in MGUS comprises in two mechanisms: the first and most important mechanism consists of immunoglobulin deposition by receptor-mediated endocytosis into tubular and glomerular cells after the aberrant protein has been excreted in the urine [7]; the second results from the immunoglobulin acting as a local antibody [8]. MGUS affects over 3% of Caucasian population >50 years [9] and it is 2–3 times more frequent in Africans and African Americans [10]. Men are more affected than women [9].

Amyloidoses are a rare group of systemic disorders caused by extracellular deposition of abnormal protein (amyloid) in multiple organs [11, 12]. The most affected

organs are the kidney and heart [13]. There are several types of amyloidoses [14]:

- amyloidosis with light chain deposits (AL amyloidosis) is diagnosed in most cases and presents proteins that are fragments of circulating immunoglobulins synthesized by plasmocytes;

- amyloidosis induced by accumulation of serum amyloid A (AA amyloidosis) consists mostly in deposited material of an acute phase reactant – serum amyloid A protein (SAA), generated by a chronic inflammation status, as seen in rheumatoid arthritis and Crohn's disease [15, 16];

- heavy chain deposition disease (AH amyloidosis).

In case of suspected amyloidosis, tissue biopsy is essential for the diagnosis. If the kidney is not involved, then the biopsy must be sampled from different sites like subcutaneous abdominal fat or rectum (positive >80%) [11, 17]. Regarding AL amyloidosis, specifically, diagnostic testing also involves serum and urine protein immunofixation electrophoresis that has a high sensitivity for the monoclonal component [18], serum free light chains, and bone marrow examination.

The term of monoclonal gammopathy with renal significance (MGRS) was introduced in 2012 by the *International Kidney and Monoclonal Gammopathy Research Group* to define the group of patients with MGUS and renal involvement [19, 20]. Renal lesions in MGRS are classified depending the type of monoclonal protein deposits [19]:

- organized: fibrillar deposits (Ig-associated amyloidosis, fibrillary glomerulonephritis); microtubular deposits (monoclonal cryoglobulinemia, immunotactoid glomerulopathy); crystal inclusions (light chain proximal tubulopathy, crystal-storing histiocytosis).

- non-organized: monoclonal immunoglobulin deposition disease and monoclonal gammopathy-associated proliferative glomerulonephritis.

Most patients with MGRS have high risk to progress to end-stage renal disease [21]; in addition, graft recurrence is common [22–24]. Therefore, in contrast with MGUS patients who need only periodic monitoring, aggressive treatment is recommended in MGRS patients. Renal biopsy is mandatory in any case of MGUS having renal manifestations, and the treatment is determined by the type of renal injury and the type of the clone producing the monoclonal immunoglobulin [25].

Aim

The purpose of this case report is to emphasize the importance of kidney biopsy in the diagnosis and treatment of monoclonal gammopathies of undetermined significance with impaired renal function.

Case presentation

A 44-year-old female (C.M.) non-smoking patient had been recently diagnosed with dyslipidemia, hypertension and proteinuria and was referred to the Department of Nephrology, “St. John” Emergency Clinical Hospital, Bucharest, Romania (Medical Record No. 25828/16.11.2016), presenting the following symptoms: bilateral edema of the lower extremities, palpebral edema, decreased diuresis and mild bilateral lumbar pain. Her personal history was not significant. For this case, the written informed consent was completed by the patient and Approval from Ethic Committee of the Hospital was obtained (No. 2117/30.01.2017). The symptoms had a gradually onset, 1–1.5 months before the presentation to the nephrologist. Serum analysis revealed an elevated platelet count of $668 \times 10^3/\text{mm}^3$, a serum creatinine of 1.35 mg/dL, mild hypocalcemia with a total calcium of 8 mg/dL (8.96 mg/dL when adjusted for albumin levels), a cholesterol level of 580 mg/dL and increased triglycerides (345.67 mg/dL). Total serum proteins were 5.07 g/dL with an albumin concentration of 2.8 g/dL. Liver function tests were within normal range. Complement fractions C3 and C4, as well as dsDNA (double stranded DNA) serum levels, were normal. Urinalysis revealed nephrotic range proteinuria (3.56 g/24 h), Bence–Jones proteins, hematuria and a positive urine culture for *Klebsiella* sp. The abdominal ultrasonography showed:

- kidneys of normal size with lengths between 11–12 cm and normal morphology;
- mild hepatomegaly, and normal spleen diameter.

Cardiac ultrasound indicated slight apical hypokinesia, an ejection fraction of 50%, no valvular abnormalities nor pericardial effusion. Lung X-ray was normal and skull X-ray presented no osteolytic lesions. Renal biopsy highlighted amorphous mesangial deposits with partial or total lumen occlusion, fibrillar amyloid deposits in the glomerular basement membrane (GBM) and tubular basement membrane (TBM) (Figure 1), and podocyte

effacement (Figure 2). Immunofluorescence was intensely positive for κ chains in the interstitium and glomeruli (Figure 3); moderate expression of λ chains and IgG in the glomeruli, and C3c fragments with granular disposition were also noticed. Therefore, diagnosis of renal amyloidosis was confirmed.

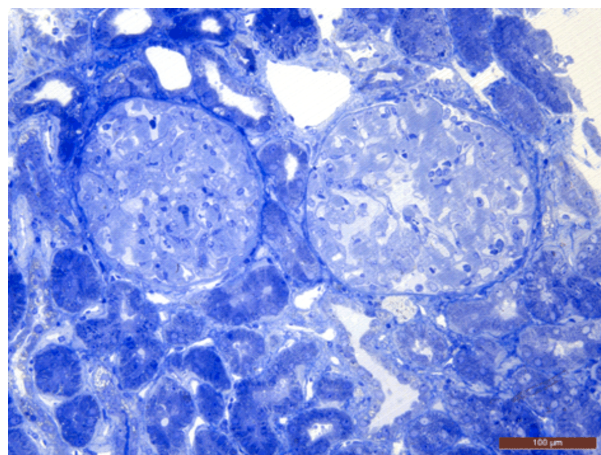


Figure 1 – Optic microscopy. Toluidine blue staining showing glomerular amorphous deposits within the capillary walls, with partial or total lumen occlusion ($\times 400$).

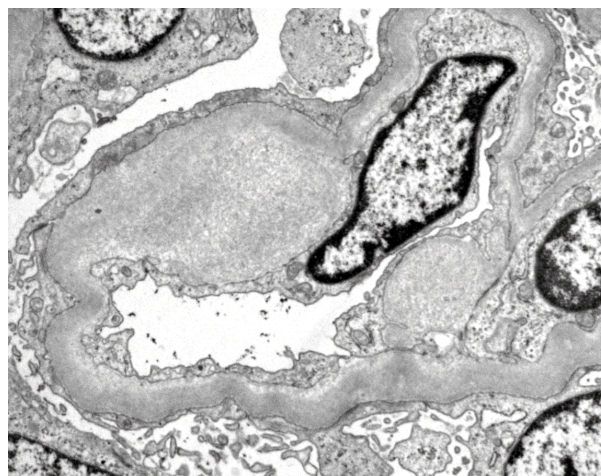


Figure 2 – Ultramicroscopic aspect. Glomeruli with fibrillar deposits in the GBM. Podocyte effacement ($\times 5000$).

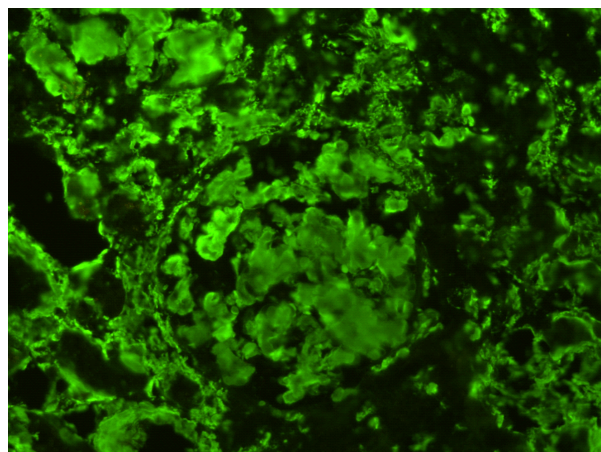


Figure 3 – Immunofluorescent staining. Intense fluorescence of kappa chains in the interstitium and glomeruli ($\times 400$).

Considering our experience from a previous study regarding N-terminal pro-brain natriuretic peptide (NT proBNP) value in renal patients [26], serum T-troponin and NTproBNP were also monitored, but they were within the normal limits. The patient was referred to a Department of Hematology, where bone marrow aspiration and biopsy revealed 7–8% CD138+ plasmocyte infiltration with a $\kappa/\lambda = 6/1$, and without any amyloid deposition in the analyzed specimen, as shown by staining with Congo red, suggesting the diagnosis of MGRS. Considering the results, the patient received pharmacological treatment, which consisted of lipid lowering agents, loop diuretic, ACE (angiotensin-converting enzyme) inhibitor, anti-platelet therapy, antibiotics. The patient also received specific chemotherapy, and considered for autologous hematopoietic stem cell transplantation.

Discussion

Amyloidoses are diseases in which circulating proteins aggregate and form fibrils that deposit in tissues causing progressive organ dysfunction. The median age of diagnosis is 60 years and some studies report a male predominance [27]. As is the case of our patient, in AL amyloidosis, the kidney is frequently affected and the clinical manifestations include nephrotic range proteinuria, edema and progressive renal failure. However, several atypical features of the clinical picture drew attention in our case: female gender, younger age-onset, no other organ affected by amyloidosis, coexistence, on kidney biopsy, of fibrillar amyloid deposits with κ chains, and presence of Bence–Jones proteinuria. The bone marrow biopsy showed only mildly increased of plasmocyte infiltration (7–8%), suggesting a MGUS. It has only recently become apparent that MGUS, which was thought to be a relatively benign hematological disorder, can have malignant consequences in respect to cardiac and renal function, especially in hemodialysis population [28, 29]. Renal involvement changes the prognosis of MGUS and requires specific therapeutic strategies to prolong kidney function and patient's survival; as we already stipulated, the new term to define MGUS with renal involvement is MGRS, as *International Kidney and Monoclonal Gammopathy Research Group* proposed [20].

Clinical manifestations of MGRS may vary, depending on the location and distribution of the amyloid deposits: deposits which are located primarily around the glomerular capillaries and mesangium will cause nephrotic syndrome (imposing the differential diagnosis with diabetic nephropathy) [30, 31], whereas infiltration of the tubular basement membranes and peritubular capillaries will lead to various tubule-interstitial nephropathies (*i.e.*, Fanconi syndrome) [32, 33]. In our case, amyloid deposition in the GBM and mesangium caused nephrotic range proteinuria, which became clinically apparent when edema ensued.

Since MGUS progresses more slowly to a truly malignant hematological disorder, treatment is not usually initiated upon diagnosis [34]. However, when end-organ damage is present adequate intervention is required to suppress the aberrant cellular clones and improve organ function and patient's survival [35, 36]. In this case, appropriate chemotherapy will be required to prevent

further renal function decline and disease progression. Traditional chemotherapeutic drugs include Melphalan, Cyclophosphamide, Bortezomib or Thalidomide [11, 17]. In addition, autologous hematopoietic stem cell transplant is considered to be beneficial, as it will help resolve the plasma cell dyscrasia [20, 37–40].

Conclusions

This case illustrates the importance of distinguishing MGUS from MGRS, since these diseases have the same etiology but very different outcomes and therapy strategies. Physicians must promptly diagnose and treat MGRS since it can have important consequences on patient's survival.

Conflict of interests

The authors declare that they have no conflict of interests.

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