

## C3 glomerulopathy: a rare kidney histological presentation of multiple myeloma

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Received for publication: Nov 24, 2017

Accepted in revised form: Jan 28, 2017

### ABSTRACT

C3 Glomerulopathy is a rare disease caused by abnormal control of the alternative complement pathway, resulting in a predominant glomerular C3 deposition. Its association with multiple myeloma has been reported in recent literature. We present a case of a 66-year-old women, referred for a nephrology consultation with a stage 4 chronic kidney disease, microhematuria, leukocyturia, sub-nephrotic range proteinuria (1.3 g/24hours), albumin 3.7 g/dl and dyslipidemia. She had been previously studied in a Hematology consultation for a normocytic anemia and an IgG Kappa monoclonal gammopathy, with 16% of plasma cells in bone marrow aspiration, but no hypercalcemia or lytic bone lesions. Autoimmune tests (ANCA, ANA, Anti-dsDNA antibody), C3 and C4 were negative. Eight months later, the patient complained of hypertension and edema, and presented a mild decrease in serum C3 (0.86 g/L [0.90-1.80]) and progressive nephrotic proteinuria (from 4.5 to 6.1 g/24h), with hypoalbuminemia. A kidney biopsy was performed, and we found mild chronic non-specific glomerular and tubule-interstitial findings, on light microscopy, and mesangial C3 deposits (+++), without immunoglobulin deposits, on immunofluorescence. Immunofluorescence with protease-digested paraffin sections was also negative. Genetic study found no complement gene mutation. She was treated with prednisone 1mg/Kg/day, with a favorable clinical and laboratorial response, but whether this treatment is enough it is still being pondered between nephrologists and hematologists.

**Key Words:** complement, C3 glomerulopathy, multiple myeloma

**Abbreviations:** **C3G:** C3 Glomerulopathy; **C3GN:** C3 glomerulonephritis; **C3NeF:** C3 nephritic factors; **CFH:** Hereditary complement factors H; **CFI:** Complement factors I; **DDD:** Dense deposit disease; **EM:** Electron microscopy; **ESRD:** End-stage renal disease; **GBM:** Glomerular basement membrane; **IF:** Immunofluorescence; **MCP:** Membrane cofactor protein; **MGRS:** Monoclonal gammopathy of renal significance; **MM:** Multiple myeloma.

### INTRODUCTION

Renal impairment is a common complication of monoclonal gammopathies, including multiple myeloma. Monoclonal gammopathy of undetermined significance (MGUS) presents with less than 10% plasma cell infiltration in the bone marrow and absence of end organ damage<sup>1</sup>. On the other hand, multiple myeloma (MM) is defined, according to International Myeloma Working Group Recommendations, by clonal

bone marrow plasma cells  $\geq 10\%$  and any one or more of the following myeloma-defining events: evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, such as hypercalcemia, renal insufficiency with creatinine  $>2$  mg/dl or GFR  $< 40$  ml/min, anemia with Hb  $< 10$  g/dl and bone lesions; any one or more of biomarkers of malignancy (clonal bone marrow plasma cells  $\geq 60\%$ , involved/uninvolved serum free light chains ratio  $\geq 100$  and  $< 1$  focal lesions on MRI studies)<sup>2</sup>.

Recently, the term monoclonal gammopathy of renal significance (MGRS) was introduced to discriminate a group of kidney disorders caused by a monoclonal immunoglobulin that is secreted by a nonmalignant or premalignant B cell or plasma cell clone, without meeting the definition of multiple myeloma. This group of kidney diseases include lesions with: **organized deposits** (immunoglobulin light chain amyloidosis, immunoglobulin heavy chain amyloidosis, immunoglobulin light and heavy chain amyloidosis, type I and type II cryoglobulinemias and immunotactoid glomerulopathy, light chain proximal tubulopathy, crystal-storing histiocytosis, and cryocrystalglobulinemia), **nonorganized deposits** (Randall type monoclonal immunoglobulin deposition disease and non-Randall type proliferative glomerulonephritis with monoclonal immunoglobulin deposits) or **lesions without deposits** (thrombotic microangiopathy associated with monoclonal gammopathy). Fanconi syndrome is also a tubular disorder that is included in MGRS<sup>3</sup>.

The most frequent monoclonal gammopathy with renal impairment is MM<sup>1</sup>. Approximately 50 percent of patients with MM experience acute (or subacute) kidney injury or chronic kidney disease during the course of their disease, but proteinuria or nephrotic syndrome can also occur<sup>4</sup>. A case series of 190 patients with MM who underwent kidney biopsy between 1997-2011, showed that the most common paraprotein-associated lesions were light chain cast nephropathy (33%), monoclonal immunoglobulin deposition disease (22%), and amyloidosis (21%)<sup>5</sup>.

C3 glomerulopathy (C3G) has also been associated with monoclonal gammopathy, including MM<sup>6</sup>. This entity was defined in 2012 and it is characterized by dominant C3 deposits (without deposits of C1q, C4 or minimal or no deposits of immunoglobulins) and variable light microscopy aspects<sup>7,8</sup>. Its pathogenesis involves an excessive activation of the alternative complement pathway, resulting in predominant C3

glomerular deposits. The incidence of C3G is approximately 1 per million per year, and it can be found in 1% of all renal biopsies<sup>6,9</sup>.

It has been hypothesized that genetic, acquired or immunologic causes could affect the regulators of the alternative pathway of the complement, leading to the hyperactivity of this pathway<sup>7,10</sup>.

Genetic factors, that explain roughly a quarter of C3G, include mutations in the complement regulatory protein factor H (CFH), factor I (CFI) and CD46 (also termed membrane cofactor protein, MCP). Genomic rearrangements, within the complement factor H-related genes (CFHR1, CFHR2, CFHR3, CFHR4, CFHR5), were also reported in familial glomerulopathies<sup>8</sup>.

The commonest acquired factors associated with C3G are C3 nephritic factors (C3NeFs), autoantibodies that stabilize the C3 convertase, preventing its inactivation by factor H<sup>8</sup>. Usually, patients with a C3NeF with or without a pathogenic genetic variant, have lower levels of circulating C3. However, there are other acquired causes of C3G, such as monoclonal gammopathy or anti-factor B and anti-factor H autoantibodies. All ages can be affected by C3G and recently more cases have been reported in the elderly patients due to its association with monoclonal gammopathy<sup>6</sup>. A renal biopsy is needed to diagnose C3G, and immunofluorescence (IF) microscopy and/or electron microscopy (EM) are essential<sup>9</sup>.

## ■ CASE REPORT

A 66-year-old Caucasian female patient was referred to our nephrology consultation with a stage 4 chronic kidney disease (serum creatinine 2.0 mg/dl for more than 3 months; GFR 23.9 ml/min/m<sup>2</sup>, CKD-EPI), anemia, microhematuria (RBC  $> 100$ /hdf), leukocyturia (75 leukocytes/hdf), sub-nephrotic range proteinuria (1.3 g/24hours), albumin 3.7 g/dl and dyslipidemia (total cholesterol 247 mg/dl, LDL 185 mg/dl and triglycerides 172 mg/dl). There was no evidence of urinary infection. She had already performed a renal ultrasound that showed normal-sized kidneys, slightly decreased cortical thickness and hyperechogenicity of both kidneys' parenchyma.

The patient had been followed up in a Hematology consultation due to a multifactorial normocytic anemia, with hemoglobin  $< 10$  g/dl, associated with iron

and folic acid deficiency, chronic gastritis and CKD, but also with an IgG Kappa monoclonal gammopathy. The proteinuria in the urine protein electrophoresis presented a glomerular pattern. A bone marrow aspiration was performed and revealed 16% of plasma cells. There was no evidence of hypercalcemia or lytic bone lesions. She presented a serum IgG of 16 g/l (normal range 7.0-16.0), serum kappa free light chains of 43.9 mg/L (normal range 6.70-22.40) and a serum free kappa/lambda chains ratio of 0.85 (normal range 0.31-1.58). Although our patient fulfilled the MM

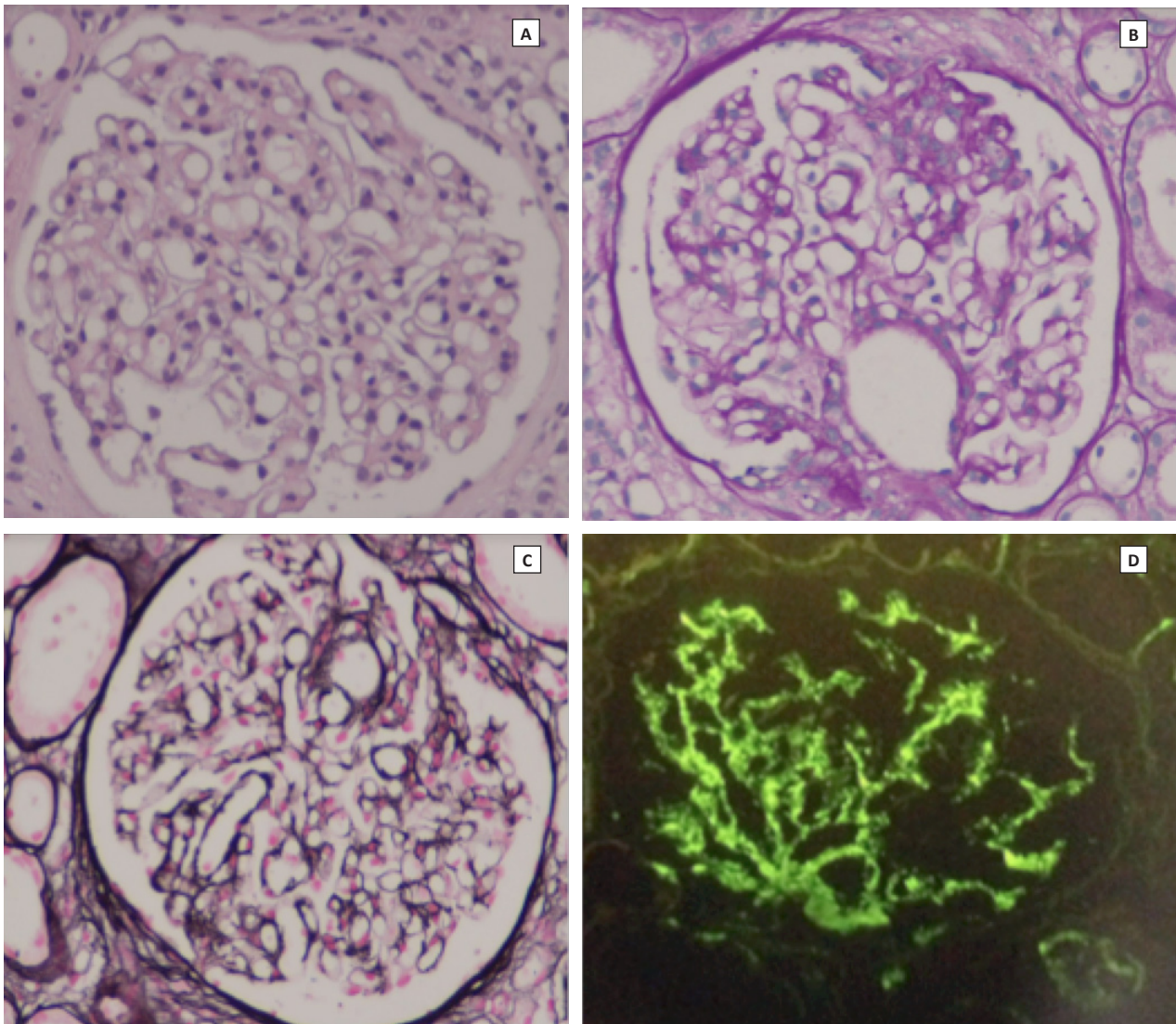
criteria, Hematology considered that a conservative approach, with vigilance of the disease progression, would be the best option for the patient considering her frailty.

Autoimmune tests (ANCA, ANA, Anti-dsDNA antibody), C3 and C4, were negative and urine cytology was negative for neoplasm.

Eight months later, the patient developed hypertension and moderate edema of the lower limbs. By that

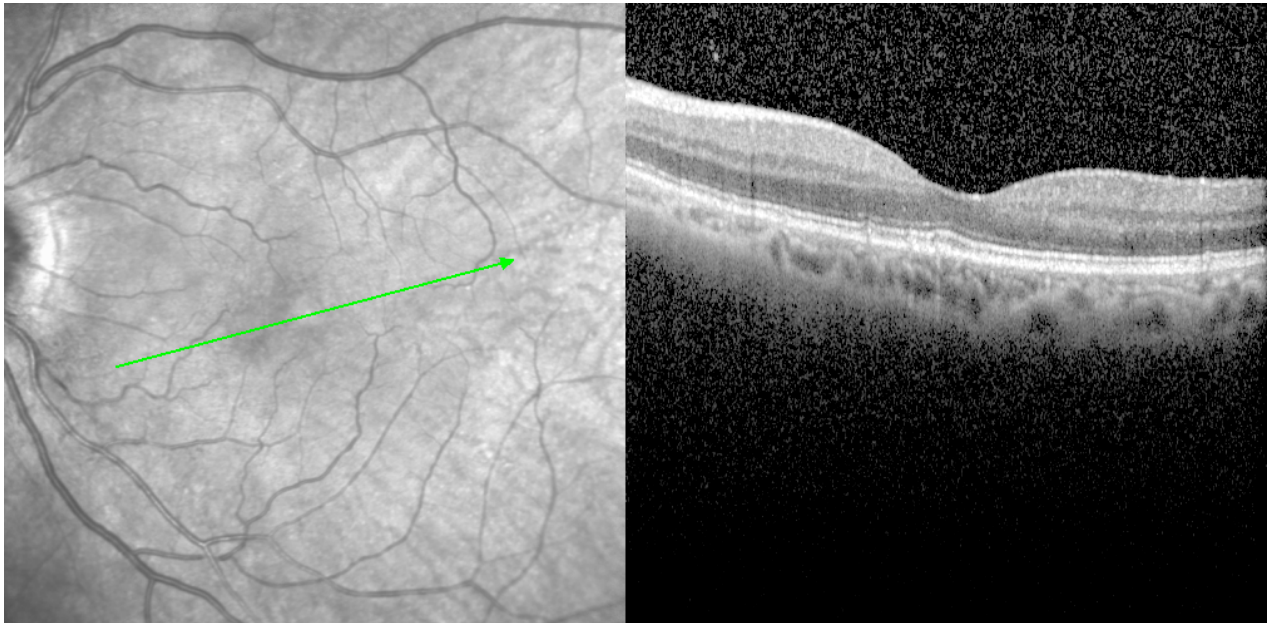
**Figure 1**

(A) Glomerulus mild hypercellularity, Hematoxylin-eosin, x400; (B) Segmental sclerosis of the glomerulus, PAS, x400; (C) No evidence of reduplication of the GBM, Methenamine Silver Stain, x400; (D) Granular mesangial and capillary wall deposits of C3 (+++), immunofluorescence microscopy, x100.



**Figure 2**

Retinal Drusen. Optical Coherence Tomography (OCT)



time, she presented a progressive nephrotic range proteinuria (from 4.5 g to 6.1/24h urine), with hypoalbuminemia of 3.3 g/dl, stable serum creatinine of 2.0 mg/dl, and a mild decrease in serum C3 (0.86 g/L [0.90-1.80]). A kidney biopsy was performed, which showed mild chronic non-specific glomerular and tubulointerstitial findings (mesangial hypercellularity, glomerulus focal segmental sclerosis and chronic interstitial fibrosis), on light microscopy. Immunofluorescence (IF) microscopy revealed diffuse granular C3 deposits (+++) in the mesangium and capillary walls, with immunoglobulin deposits remarkably absent (even after repeating the IF) (Figure 1). An IF study with protease-digested paraffin sections was also negative for immunoglobulin deposits.

Genetic study revealed no complement gene mutation, such as CFHR5 mutation, mutation screening of complement regulatory genes (CFH, CFI, CD46), activation protein genes (C3, CFB) and assessment of copy number variation across the CFH-CFHR locus. C3NeF wasn't evaluated (not available) and factor H autoantibodies were negative.

Regarding extrarenal abnormalities, we found retinal Drusen in Optical Coherence Tomography (OCT) (Figure 2).

The histologic findings and laboratory tests were discussed with the hematologists, which maintained their previous position of a conservative approach.

In order to control the nephrotic syndrome, she was treated with enalapril 10 mg/day, atorvastatine 20 mg/day and prednisone 1mg/Kg/day, in a progressive withdrawal regimen after one month. There was a favorable clinical and laboratorial response, with a decrease in 24h proteinuria (3g after 15 days, 1.3 g after 2 months, 0.8 g after 6 months), an increasing albumin (from 2.6 mg/dl to 3.4 g/dl), a decrease in serum IgG (from 16 g/dl to 3.9 g/dl after 2 months) and a decrease in serum free kappa light chains (from 43.9 to 34.2 mg/L after 3 months). During this period, the patient maintained stable kidney function. A second bone marrow aspiration was performed 9 months after the initiation of the corticoid therapy and revealed 0.2% of plasma cells.

## ■ DISCUSSION

We report a case of C3G, associated with a MM. It has been hypothesized that C3G may be a new variant of renal manifestation in MM. However, it is an ultra-rare

disease, and in our case report, it was an unexpected diagnosis<sup>11</sup>. No other cause for our patient's renal impairment was identified.

In C3G, the pattern seen on light microscopy may show a broad range of features—membranoproliferative pattern, mesangial proliferation, endocapillary proliferation, leukocyte infiltration and/or crescents or even normal glomeruli<sup>8,12</sup>. Therefore, the diagnosis can only be made by IF, as described in our patient. Immunoglobulins proteins occasionally show false negative staining by routine IF. We performed IF on protease-digested paraffin-sections. This can “unmask” these deposits, in order to confirm that there were no immunoglobulins deposits in the glomeruli<sup>12</sup>. The negative result of this specific IF in our patient confirmed the diagnosis of C3G.

Based on EM, this disease can be subclassified as dense deposit disease (DDD), with very dense C3 deposits, or C3 glomerulonephritis (C3GN), with less dense deposits<sup>10</sup>. Subepithelial hump-like deposits, similar to those in post-infectious glomerulonephritis, can also be seen [8]. One limitation in our evaluation was not having performed EM, in order to establish DDD or C3GN, which is not available in our Center.

There are several reports of monoclonal gammopathy and a few cases reports of multiple myeloma associated with C3G. The mechanism is unknown, but it has been suggested that the monoclonal immunoglobulin may act as an autoantibody to complement components, activating the alternative complement pathway<sup>6,8</sup>.

Clinical presentation is variable. The majority of patients have a chronic and indolent course of the disease but some patients may present a rapidly progressive crescentic glomerulonephritis<sup>6,10</sup>. At presentation, proteinuria (with or without nephrotic syndrome), hematuria, nephritic syndrome, rapidly progressive glomerulonephritis or hypertension, can occur. Retinal Drusen, the accumulation of lipids and complement-rich proteins in the retina, are recognized as an extrarenal manifestation of C3G but it's not a pathognomonic feature, particularly at the age of this patient, as they are commonly seen in age-related macular degeneration<sup>9</sup>.

Although C3G is a recent entity, a 10-year renal survival of approximately 50% was described and there are several reports of recurrence even after kidney transplantation<sup>6,9</sup>.

There is still no consensus regarding the treatment of C3G, as this entity is rare, its etiopathogenesis has only recently been partially understood and there are no prospective randomized clinical trials<sup>7</sup>. According to 2015 Kidney disease: Improving Global Outcomes (KDIGO) Controversies Conference, it is recommended that all patients should receive optimal blood pressure control (priority agents such as angiotensin converting enzyme inhibitors and angiotensin receptor blockers) and that patients with “moderate” severity of the disease (urine protein >500 mg/24 hours despite supportive therapy, moderate inflammation on renal biopsy or recent rise in creatinine), should be treated with prednisone or mycophenolate mofetil. Methylprednisolone pulses should be set aside for the “severe” disease (urine protein >2g/day or rapidly progressive disease)<sup>9</sup>. Other treatments include antithrombotics, anticoagulants, plasmapheresis and eculizumab (an humanized antibody anti-C5 that has been used in patients with elevated levels of the soluble membrane attack complex). However, when there is evidence of an underlying disease, such as a monoclonal gammopathy including multiple myeloma, it has been suggested that its treatment is important as part of the treatment of C3G<sup>11,13</sup>.

The treatment of MGRS is determined primarily by the pathologic type of renal injury, the nature of the clone (either plasma cell, B cell, or lymphoplasmacytic) that is producing the nephrotoxic monoclonal immunoglobulin, and the likelihood of reversing existing renal damage or preventing further renal injury. However, an approach that employs chemotherapy against the pathologic clone is recommended<sup>13</sup>. The treatment of MM with renal impairment depends on its presentation. However, supportive measures with high fluid intake (without causing hypervolemia) and antimyeloma therapy is crucial. Renal outcomes of patients with MGRS and MM (with or without association with C3G) are closely associated with the hematologic response to chemotherapy<sup>2,14</sup>.

Renal impairment in MM is associated with a higher rate of treatment-related toxicity, early mortality and reduced overall survival. New therapeutic agents such as immunomodulators (thalidomide, lenalidomide and pomalidomide) and proteasome inhibitors (bortezomib and carfilzomib) improved not only the renal outcome but also the overall survival of patients with MM<sup>15</sup>. Hematopoietic cell transplantation should also be considered.

All this information was discussed between nephrologists and hematologists before and after the

initiation of the corticoid therapy, but no other specific treatment was given despite her progressive renal impairment, considering her frailty but also her clinical and laboratorial improvement under this medication.

Despite the good hematologic response of this patient, with only corticoid therapy, and her stable kidney function, it is still unknown whether this treatment will be enough to control the disease or to prevent its recurrence. We will maintain a multidisciplinary approach in our patient follow-up in order to adjust patient's therapeutic strategy and maintain vigilance of the disease progression or any other complications that may arise.

**Disclosure of potential conflicts of interest:** none declared

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